UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

March 13, 2001

OFFICE OF
THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

Note to the Reader:

The attached draft report is a draft report of the Science Advisory Board (SAB). The draft is still undergoing final internal SAB review, however, in its present form, it represents the consensus position of the panel involved in the review. Once approved as final, the report will be transmitted to the EPA Administrator and will become available to the interested public as a final report.

This draft has been released for general information to members of the interested public and to EPA staff. This is consistent with the SAB policy of releasing draft materials only when the Committee involved is comfortable that the document is sufficiently complete to provide useful information to the reader. The reader should remember that this is an unapproved working draft and that the document should not be used to represent official EPA or SAB views or advice. Draft documents at this stage of the process often undergo significant revisions before the final version is approved and published.

The SAB is not soliciting comments on the advice contained herein. However, as a courtesy to the EPA Program Office which is the subject of the SAB review, we have asked them to respond to the issues listed below. Consistent with SAB policy on this matter, the SAB is not obligated to address any responses which it receives.

1. Has the Committee adequately responded to the questions posed in the Charge?
2. Are any statements or responses made in the draft unclear?
3. Are there any technical errors?

For further information or to respond to the questions above, please contact:

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SCIENCE ADVISORY BOARD

DIOXIN REASSESSMENT REVIEW COMMITTEE (DRRS)

EXECUTIVE COMMITTEE REVIEW DRAFT 1

March 12, 2001

FOR REVIEW ONLY -- DO NOT QUOTE OR CITE

PLEASE NOTE THAT THIS DRAFT IS ALSO UNDERGOING CONCURRENT FINAL REVIEW BY THE DRRS. IT IS EXPECTED THAT ANY CHANGES WILL BE MINOR. A FINAL DRAFT WILL BE AVAILABLE BY MARCH 21, 2000

April xx, 2001

Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Review of the revised sections (Dose Response Modeling, Integrated Summary and Risk Characterization, and Toxicity Equivalency Factors) of the Office of Research and Development's Reassessment of Dioxin.

Dear Ms. Whitman:

In April 1991, EPA announced that it would conduct a scientific reassessment of the potential health risks of exposure to dioxin and related compounds. The reassessment addressed the emerging scientific knowledge of the biological, human health, and environmental effects of these substances, evaluating in particular significant advances in the scientific understanding of mechanisms of dioxin toxicity, the potential for carcinogenic, and other adverse health effects of dioxin on people, human exposure pathways, and the adverse effects of dioxin on the environment.

The reassessment led to the publication of the draft document *Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-p-Dioxin (TCDD) and Related Compounds* in 1994. In 1995, EPA's Science Advisory Board (SAB) reviewed this draft, and issued a report (EPA-SAB-EC-95-021) with the following four key findings:

a) Substantive changes were needed in two sections in the reassessment documents: the chapter on Dose Response Modeling (Chapter 8) and the Risk Characterization document (identified as Chapter 9 in a previous draft).

b) EPA should develop a new chapter on toxicity equivalence factors (TEFs) to consolidate the discussion and scientific information on the use of TEFs for dioxin and related compounds.

c) The health and exposure sections (Chapters 1–7) did not require significant changes, and there was no need for further SAB review as long as EPA updated these sections with any relevant new information before finalizing them.

d) The revised chapters on Dose Response Modeling and Risk Characterization and the new chapter on TEFs should undergo external peer review prior to the SAB's re-review of these issues.

After EPA completed its revisions, and addressed the comments of several external peer review panels, the revised sections of the Reassessment were submitted to the SAB for review in late September, 2000. The SAB Dioxin Reassessment Review Subcommittee (DRRS) (of the SAB Executive Committee) subsequently met on November 1 and 2, 2000 to review those sections of the Reassessment document noted above (in addition, the DRRS met via public teleconference on January 23, 2001, to discuss further several issues which had not been resolved during the report preparation process). Per usual SAB practice, a Charge (see Section 2.2 of the enclosed report) for the November meeting was developed jointly by EPA staff, SAB staff, and the Chair of the DRRS. The Charge comprised 21 enumerated questions, some of which incorporated two to four sub-elements. The enclosed report addresses each of these questions in detail; however, because of the level of detail involved, this letter will summarize the Subcommittee's findings on the major issues, rather than address each element of the Charge.

A majority of the Subcommittee agreed that the EPA need not submit a further revision of the document for SAB review. This decision was not reached because the DRRS believed that the current evaluation reached fully supportable scientific conclusions on every issue, but because they believed that there would still not be adequate information available within the next several years to significantly reduce the large amount of uncertainty inherent in any current risk assessment of dioxin and related chemicals.

The DRRS identified the key issues that they want EPA to consider when they revise and finalize the chapters 8 and 9 of the Reassessment document, and the new TEF chapter. The Subcommittees's views on these issues follow.

Regarding designating dioxin as a human carcinogen, the DRRS agrees that causal associations have been established between exposure to TCDD and increased cancer incidence for some types of cancers in some species of laboratory animals. The Subcommittee agrees that TCDD acted as a cancer promoter rather than as a cancer initiator in these studies. The Panel also agrees that the body of such results is sufficient to satisfy the criterion for compelling evidence of carcinogenicity in laboratory animals for TCDD, if the term "carcinogen" is applied to tumor promoters as well as tumor initiators. There is a lack of consensus in the DRRS with regard to whether TCDD satisfies EPA's 1996 draft cancer Guidelines criteria for a human cancer hazard. There is disagreement about the strength of the epidemiological data indicating that dioxin is carcinogenic in humans, as well as the scientific data demonstrating similar modes of action in humans and laboratory animals. The Subcommittee Members differ on their confidence that the reported statistically significant associations between exposure and cancer endpoints reported for the occupationally-exposed cohorts can be concluded to be causal. Some Members support the classification of TCDD as a human carcinogen. However, most DRRS Members do not support the classification of TCDD as a human carcinogen, citing a) the lack of a consistent carcinogenic response across the various epidemiological studies; b) the small relative risks observed in each study; c) the possible impact of confounding factors; d) the lack of understanding of the mechanism of action; and e) the increase relied upon by EPA is in total number of tumors (a response not heretofore attributed to any chemical carcinogen).

The DRRS has several recommendations regarding the risk assessment methodology for dioxin. In the present draft report, two fundamentally different approaches are used for cancer and non-cancer risk assessment. For cancer it is assumed that no exposure is without risk, and an upper bound estimate of risk is developed using a linear dose-response. In contrast, risk estimates are not developed for non-cancer responses; instead a margin of exposure (MOE) approach is applied in which environmental exposures are compared to a dose(also called the "point of departure") that is intended to correspond to the lower end of the dose range where adverse effects have been observed. The DRRS has several concerns about this dual approach. In view of the underlying science, the use of fundamentally different quantitative approaches for cancer and non-cancer does not appear to be justified. The Subcommittee was concerned that presentation of quantitative estimates of risk only for cancer might focus unwarranted attention upon cancer at the expense of non-cancer risks. Consequently, the Panel recommends that the Agency develop a similar approach for all adverse health effects of dioxin. The Panel also recommends that, in addition to the point of departure, an RfD (reference dose) also be calculated. Such a calculation could provide: a) a useful societal exposure goal: b) an informative perspective on potential dioxin risks; and c) comparisons with other substances for which a RfD has been calculated, while not precluding use of the MOE approach.

The calculation of a cancer potency factor was a focus of considerable discussion. The draft EPA document used a linear dose extrapolation model to derive an upper bound cancer potency factor. Some Members argue that the Agency should also derive alternative cancer potency factors using other plausible models, and that these would generally predict lower risks at all doses. Other Members argue that fitting the available data to more complex models cannot be justified on statistical grounds. Because of these limitations, as noted above, the DRRS recommends against reliance upon a particular potency factor or quantitative estimate of risk at the present time.

The majority of the Subcommittee had concerns about the cancer risk estimates that the Agency has stated could be associated with background doses of dioxins. In light of their lack of confidence in the cancer potency factor and the uncertainty around the TEFs for many of the dioxin-like chemicals (e.g., PCBs), they did not believe that it was appropriate for the Agency to characterize the risks to be

about 1 in 1,000 for the average American on a high animal fat diet. This estimate tends to place too much confidence in our ability to accurately predict cancer risks at low doses, especially for a group of chemicals for which we have only a limited understanding of the mechanism of action or the differences in response between animals and humans.

Most DRRS Members were concerned that the Reassessment Document downplays the potential non-cancer risks posed by these chemicals at background doses relative to the potential cancer risks. The Subcommittee found it difficult, however, to ascertain the degree of severity of the non-cancer public health hazard because so many different endpoints and different animal studies gave conflicting results at comparable doses. The evaluation of the non-cancer data would have been much more transparent if the Agency had presented effective dose (ED) or point-of-departure information for specific congeners and health-related responses. The DRRS recommends that point-of-departure information and RfDs be calculated for specific responses or classes of responses and that they be presented in the revised document.

The application of TEFs received a significant amount of discussion. Some Members expressed concern over the fact that (as noted in the Reassessment document) only 10% of current doses are due to 2,3,7,8 TCDD, yet this is the chemical for which we have 95% of the cancer and non-cancer risk data. In short, we have to assume that 2,3,7,8 -TCDD risk estimates (cancer and non-cancer) apply to the (approximately) 30 dioxin-like chemicals, despite their differences in metabolic pathways and half-lives in tissues. On the other hand, the majority of the Subcommittee noted that the TEF approach is well accepted internationally, that no alternative approach is currently available, and that the empirical data support the approach. Because about 20% of the uptake in the diet is due to the PCBs, those Members concerned about current TEF values recommended that the associated risk estimates for PCBs be better characterized, provided the relevant data are available. They were also concerned that the current document presented conclusions on TEF values that could be interpreted as being much more robust and scientifically supportable than is justified by the available data. Other Members felt that the Agency should not

be faulted for its interpretations of the data, because the current state of knowledge, as recognized by numerous authorities, offers no feasible alternative.

The DRRS agreed that the proposed dose metrics, such as body burden, steady-state blood level, or area under the curve were superior to using the traditional mg/kg-day metric. However, the majority of this Panel also agreed with the Agency's July peer review panel recommendation that a better justification for using a certain dose metric was needed. The Subcommittee urges EPA to provide examples of how different dose metrics might apply to specific toxic endpoints. Finally. this concept deserves a much more complete discussion than was presented in the draft reassessment.

In setting its range of 10 - 50 ng/kg body burden as a "point of departure" for calculating a MOE for non-cancer effects, the Agency appropriately evaluated data on a variety of responses, including both biochemical and whole-organ endpoints. However, in their numerical treatment of these data the Agency relied solely upon a non-robust (e.g., subject to large variation in the estimated value depending on the input data and/or specific model assumptions and therefore questionable) definition of the ED_{01}. Since the effect of this particular approach upon the point of departure is not clear, the DRRS recommends that ED also be calculated using other definitions that are also consistent with Agency guidance. Furthermore, since the ED_{10} has generally been applied to other chemicals assessed by the Agency, these values should also be presented for comparison purpose. Regardless of the outcome of this re-analysis, the Subcommittee also recommends that the Agency give additional thought and justification regarding its selection of a method for condensing these EDs into a recommended range. Finally, the Agency's description of its calculation of ED_{01} was not sufficiently detailed to permit the calculations to be repeated. A clear and complete description of the this calculation would significantly improve the transparency and accessibility of the Reassessment.

The Subcommittee found that some additional work on the exposure assessment section is needed. Specifically, the text and tables describing the source inventory in the Summary are not consistent with the inventory information presented elsewhere in the document, and there needs to be

more careful evaluation of the sources of dioxin that make the greatest contribution to dioxin in the food chain.

Because naturally-occurring dioxin-like chemicals can be found in the diet, EPA should explore the magnitude of their biological activity, particularly for questions such as transplacental transport and their ability, *in utero*, to interfere with reproductive development, as has been documented for TCDD itself. Most Members were persuaded that some or all constituents of these families of naturally occurring chemicals do not elicit the full spectrum of dioxin-like effects. However, since these chemicals compete for the same cellular receptor (Ah) as do the 30 listed "dioxin-like chemicals" from industrial and combustion sources (although the binding affinity is much less) and their dose is orders of magnitude greater than that of these 30 agents, the Agency should provide further documentation supporting their position that these chemicals aren't significant. Since the naturally occurring dioxin-like chemicals are in the diet, and therefore have a steady-state concentration in blood and tissue, the EPA's position that their short biologic half-life makes them less biologically active was not found to be convincing and requires additional support.

There is some evidence that very low doses of dioxin may result in decreases in some adverse responses, including cancer. Although the Subcommittee did not reach any definite conclusions regarding this issue, it does believe that it deserves additional scrutiny. Consequently, the DRRS recommends that the totality of evidence concerning this phenomenon, including its potential impact on human health risk, be evaluated more thoroughly by the Agency. Similarly, any evidence that dioxin can produce adverse health effects at extremely low doses (as has been asserted for other substances that affect the endocrine system) should also be carefully evaluated.

Finally, it is important to continue to study and evaluate background levels of this family of chemicals. Even though some Members believe that the current draft assessment may overstate the likely cancer hazard, most believe that non-cancer hazards, such as impaired development, received too little attention in the document. Consistent with basic environmental policy, it is important that EPA continue to try to limit emissions (and human exposure to this class of chemicals) in view of their very

long biological and environmental persistence.

We appreciate the opportunity to review these issues, and look forward to your response.

Sincerely,

Dr. William Glaze, Chair
Science Advisory Board

Dr. Morton Lippmann, Chair
Dioxin Reassessment Review Subcommittee
Science Advisory Board

ENCLOSURE

NOTICE

This report has been written as part of the activities of the Science Advisory Board, a public advisory group providing extramural scientific information and advice to the Administrator and other officials of the Environmental Protection Agency. The Board is structured to provide balanced, expert assessment of scientific matters related to problems facing the Agency . This report has not been reviewed for approval by the Agency and, hence, the contents of this report do not necessarily represent the views and policies of the Environmental Protection Agency, nor of other agencies in the Executive Branch of the Federal government, nor does mention of trade names or commercial products constitute a recommendation for use.

Distribution and Availability: This Science Advisory Board report is provided to the EPA Administrator, senior Agency management, appropriate program staff, interested members of the public, and is posted on the SAB website (www.epa.gov/sab). Information on its availability is also provided in the SAB's monthly newsletter (Happenings at the Science Advisory Board). Additional copies and further information are available from the SAB Staff.

ABSTRACT

TO BE SUPPLIED

ROSTER

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[1] Dr. Graham participated in the public meeting and contributed to the first three drafts of this report. He resigned from the Subcommittee in March, 2001, after accepting and appointive position with the Federal Government.

[2] Present only on Day 1 of the Public Meeting

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[3] Unable to attend the Public Meeting, but participated in reviewing the Committee's report

[4] Unable to attend the Public Meeting, but participated in reviewing the Committee's report

1 EXECUTIVE SUMMARY

In April 1991, EPA announced that it would conduct a scientific reassessment of the potential health risks of exposure to dioxin and related compounds. The reassessment led to the publication of a multi-volume document titled "Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds." The draft of this document was published in 1994. In 1995, this draft was reviewed by EPA's Science Advisory Board (SAB), which issued a 1995 report (EPA-SAB-EC-95-021) with the following four key findings:

a) The review provided substantive comments on two sections in the reassessment documents: the chapter on Dose Response Modeling (Chapter 8) and the Risk Characterization document (identified as Chapter 9 in a previous draft).

b) The review recommended that EPA develop a new chapter on toxicity equivalence factors (TEFs) to consolidate the discussion and scientific information on the use of TEFs for dioxin and related compounds.

c) The review approved the health and exposure sections (Chapters 1–7), stating that there was no need for further SAB review as long as EPA updated these sections with any relevant new information before finalizing them.

d) The review recommended that the revised chapters on Dose Response Modeling and Risk Characterization and the new chapter on TEFs undergo external peer review prior to the SAB's re-review.

EPA revised the 1994 Reassessment document to address the first three findings listed above and conducted external peer reviews of the revised chapters on Dose Response Modeling (Chapter 8), the updated Integrated Summary and Risk Characterization, and the new chapter on TEFs.

After EPA completed further revisions addressing the comments of the several peer review panels, the SAB Dioxin Reassessment Review Subcommittee met on November 1 and 2, 2000 to review those sections of the Reassessment document specified in the 1995 SAB report. Per usual SAB practice, a Charge (see below) for the meeting was developed jointly by EPA staff, SAB staff, and the

Chair of the SAB Dioxin Reassessment Review Subcommittee (DRRC). Also, consistent with SAB practice, Members of the DRRC were informed that the Charge was not intended to be exclusive and that additional issues could be introduced by any Member as appropriate.

A majority of the Panel concluded that they should not ask the EPA to submit a further revision of the document for SAB review.[5] This decision was not reached because the SAB believed that the current evaluation reached fully supportable scientific conclusions, but because they believed that there would still not be adequate information available within the next several years to significantly reduce the large amount of uncertainty inherent in any current risk assessment of dioxin and related chemicals.

The Panel worked diligently to identify the key issues that they want EPA to consider when they revise and finalize the chapters 8 and 9 of the reassessment and the Summary document. The Panel's views on these key issues are as follows:

a) HUMAN CARCINOGEN DESIGNATION: EPA has designated criteria for designating a substance as a human cancer hazard in its revised carcinogen risk assessment guidelines (EPA, 1998 and 1996 (still currently in draft form)). In essence, the Agency requires that there be compelling evidence of carcinogenicity in humans or compelling evidence of carcinogenicity in laboratory animals coupled with suggestive evidence of carcinogenicity in humans and similarity of the mode of action in humans and laboratory animals. The criteria for being a likely human carcinogen are somewhat less stringent.

   The Panel agrees that causal associations have been established between exposure to TCDD and increased cancer incidence for some types of cancers in some species of laboratory animals. The Panel agrees that TCDD acted as a cancer promoter rather than as a cancer initiator in these studies. The Panel also agrees that the body of such results is sufficient to satisfy the criterion for compelling evidence of carcinogenicity in laboratory animals for TCDD, if the term "carcinogen" is applied to tumor promoters as well as tumor initiators.

[5]Panel Members who could not attend all (Ringen, McConnell, and Luster) or some (Greenlee) of the meeting contributed to the written comments contained in this document.

There is a lack of consensus in the Panel with regard to whether TCDD satisfies EPA's 1996 draft cancer Guidelines criteria for a human cancer hazard. There is disagreement about the strength of the epidemiological data indicating that dioxin is carcinogenic in humans, as well as the scientific data demonstrating similar modes of action in humans and laboratory animals.

The Panel Members differ on their confidence that the reported statistically significant associations between exposure and cancer endpoints reported for the occupationally-exposed cohorts can be concluded to be causal. Some Panel Members support the classification of TCDD as a human carcinogen. They believe that the results from studies of TCDD-exposed workers are persuasive and that the variety of studies from researchers in different countries provide limited but convincing evidence of TCDD's carcinogenicity in humans, particularly for lung cancer and soft tissue sarcomas. However, most Panel Members do not support the classification of TCDD as a human carcinogen, citing (1) the lack of a consistent carcinogenic response across the various epidemiological studies; (2) the small relative risks observed in each study; (3) the possible impact of confounders; (4) the lack of understanding of the mechanism of action; and (5) the primary increase claimed by EPA is in total number of tumors (a response not heretofore attributed to any chemical carcinogen).

With regard to the similarities in mode of action between the human and animal data, some Members of the Panel found EPA's arguments about these similarities persuasive, and concluded that TCDD is a multi-species, multi-organ, carcinogen in male and female experimental animals. However, most Panel Members hold that the key events in the causation of cancer (i.e. initiation, proliferation, and uncontrolled growth) that precede the cancer response in animals have not been observed in humans. Some Members were also concerned that bias in both human and animal studies might have overstated the case for dioxin's carcinogenicity. These Members consider that because of these limitations, the evidence for TCDD carcinogenicity in humans is not as compelling as for known human carcinogens such as cigarette smoke, asbestos, or radon.

Some Members note that the five reservations listed above may not apply to an agent that is a cancer promoter. For cancer promoters the risks might include different

cancers across populations depending on the initiating agents and timing of exposures. These Members acknowledged that the observed risks may be low if the population's exposure to an initiator is low. Improperly controlling for "confounders" that are cancer initiators could mask the true effect of a promoter. A discussion by EPA of the expected differences in results between epidemiological studies of genotoxic agents versus cancer promoters could aid in the interpretation of the epidemiological data.

b) RISK ASSESSMENT METHODOLOGY: The Panel has several recommendations regarding the risk assessment methodology for dioxin. In the present draft report, fundamentally different approaches are used for cancer and non-cancer. For cancer it is assumed that no exposure is without risk, and an upper bound estimate of risk is developed using a linear dose response. In contrast, risk estimates are not developed for non-cancer responses; instead a margin of exposure (MOE) approach is applied in which environmental exposures are compared to a dose (called a "point of departure") that is intended to correspond to the lower end of the dose range where adverse effects have been observed. The Panel has several concerns about this dual approach. Since adverse effects of dioxin are believed to be mediated by a common first step (binding to the AhR locus), use of fundamentally different quantitative approaches for cancer and non-cancer does not appear to be justified. Some Members of the Panel believed that the assumption of a linear dose response for cancer was unwarranted because dioxin is a cancer promoter rather than an initiator. The Panel was also concerned that presentation of quantitative estimates of risk only for cancer might focus unwarranted attention upon cancer at the expense of non-cancer risks. Consequently, the Panel recommends that the Agency develop a similar approach for all adverse effects of dioxin.

Concerning what this common risk assessment approach should be, it would ideally be most useful for risk managers to have quantitative estimates of the risk from low exposures, provided such estimates could be made in a reliable manner. However, the Panel believes the information base for dioxin does not allow such estimates to be reliably developed at present. As noted in c) below, Panel Members have numerous concerns regarding the quantitative estimates for cancer provided in the Agency's current draft. Consequently, the Panel recommends against reliance upon quantitative estimates of risks from very low exposures at the present time.

Traditionally, the Agency has used RfD (RfC for air contaminants) to inform decisions regarding health-based exposure guidelines. An RfD is a dose considered to be without appreciable risk, and is calculated by dividing the "point of departure" used in the MOE analysis by factors that address issues such as the potential risk at the point of departure, differences in susceptibility of animals and humans, variation in susceptibility within the human population, and various potential shortcomings in the scientific data. The Agency chose not to calculate an RfD for dioxin, stating that the resulting RfD would be below current background exposure and, therefore, would be "uninformative for risk assessment." However, an RfD reflects the agency's scientific judgment concerning potential low dose risks and the strength of the data base. Consequently, the Panel believes it can provide useful scientific information to risk managers and the general public that is not provided by the point of departure alone. The Panel therefore recommends that, in addition to the point of departure, an RfD also be calculated. Such a calculation could provide a useful societal exposure goal, could provide a useful perspective on potential dioxin risks, could facilitate comparisons with other substances for which a RfD has been calculated, while not precluding use of the MOE approach. The Panel further suggests that the Agency also consider developing separate RfD and point of departure for health effects of differing severities (e.g., cancer versus a biochemical change having limited or uncertain health consequences).

c) CALCULATION OF CANCER POTENCY FACTOR: The calculation of the cancer potency factor was a focus of considerable discussion. The Panel agreed that the actual shape of the low-dose exposure response relation cannot be determined from the available data. For this reason, the Agency used a linear dose extrapolation model to derive an upper bound cancer potency factor. Some Members argue that the Agency should also derive alternative cancer potency factors using other plausible models,and that these would generally predict lower risks at all doses. Other Members argue that fitting the available data to more complex models cannot be justified statistically. Because of these limitations, as noted above, the Panel recommends against reliance upon a particular potency factor or quantitative estimate of risk at the present time.

The Agency's calculation of the cancer potency factor is not provided in the Reassessment. Inclusion of this calculation would significantly improve the transparency and accessibility of the Reassessment.

d) CANCER RISKS AT BACKGROUND DOSES: The majority of the Panel Members had concerns about the cancer risk estimates that the Agency has stated could be associated with background doses of dioxins (on a TEQ basis). In light of their lack of confidence in the cancer potency factor and the uncertainty around the TEFs for many of the dioxin-like chemicals (e.g., the PCBs), they did not believe that it was appropriate for the Agency to characterize the risks to be about 1 in 1,000 for the average American on a high animal fat diet. This estimate tends to place too much confidence in our ability to predict accurately cancer risks at low doses, especially for a group of chemicals for which we have only a limited understanding of the mechanism of action or the differences in response between animals and humans.

e) NON-CANCER RISKS AT BACKGROUND DOSES: Most Panel participants were concerned that the Reassessment Document downplays the potential non-cancer risks posed by these chemicals at background doses relative to the potential cancer risks. The Panel found it difficult, however, to ascertain the degree of severity of the non-cancer public health hazard because so many different endpoints and different animal studies gave conflicting results at comparable doses. In some cases, doses considered "the critical ones" were for rather minor biological effects, whereas more serious effects were only observed at much higher doses. The evaluation of the non-cancer data would have been much more transparent if the Agency had presented ED or point-of-departure information for specific congeners and responses. The Panel recommends that point-of-departure information and RfDs be calculated for specific responses or classes of responses and that they be presented in the revised document.

f) TEFs: The application of TEFs received a significant amount of discussion. Some Members expressed concern over the fact that (as noted in the Reassessment document) only 10% of current doses are due to 2,3,7,8 TCDD, yet this is the chemical for which we have 95% of the cancer and non-cancer risk data In short, we have to assume that 2,3,7,8 -TCDD risk estimates (cancer and non-cancer) apply to the ~30 dioxin-like chemicals, despite their differences in metabolic pathways and half-lives in tissues. On the other hand, the majority of the Panel noted that the TEF approach is well accepted internationally, that no alternative approach is currently available, and that the empirical data support the approach (van den berg *et al*, 2000). Because about 20% of the uptake in the diet is due to the PCBs **(Will provide reference for this statement)**,

those Members concerned about current TEF values recommended that the associated risk estimates for PCBs be better characterized, provided the relevant data are available. They were also concerned that the current document presented conclusions on TEF values that could be interpreted as being much more robust and scientifically supportable than is justified by the available data. Other Panel Members felt that the Agency should not be faulted for its interpretations of the data, because the current state of knowledge, as recognized by numerous authorities, offers no feasible alternative, and, also, because current TEFs may underestimate as well as overestimate the toxic potency of TEQs (e.g., van der Plas *et al*, 2000).

g) DOSE METRICS: The Panel agreed that dose metrics, such as body burden, steady-state blood level, or area under the curve (AUC) were superior to using the traditional mg/kg-day metric. However, the majority of this Panel also agreed with the Agency's July peer review panel recommendation that a better justification for using a certain dose metric was needed. The Panel urges EPA to provide examples of how different dose metrics might apply to specific toxic endpoints. For example, whereas lifetime average body burden or AUC may be more appropriate than peak exposure for predicting cancer risks, some measure of peak exposure during pregnancy would be more appropriate for predicting the likelihood of an adverse effect upon the developing fetus. This concept deserves a much more complete discussion than was presented in the draft reassessment.

h) MARGIN OF EXPOSURE APPROACH: In setting its range of 10 - 50 ng/kg body burden as a "point of departure" for calculating MOE for non-cancer effects, the Agency appropriately evaluated data on a variety of responses, including both biochemical and whole-organ endpoints. However, in their numerical treatment of these data the Agency relied solely upon a non-robust (e.g., subject to large variation in the estimated value depending on the input data and/or specific model assumptions and therefore questionable) definition of the ED_{01}. Since the effect of this approach upon the point of departure is not clear, the Panel recommends that ED also be calculated using other definitions that are consistent with Agency guidance. Also, since the ED_{10} has been applied to other chemicals by the Agency, for comparison purposes these values should also be presented. Regardless of the outcome of this re-analysis, the Panel also recommends that the Agency give additional thought and justification regarding its

selection of a method for condensing these ED into a recommended range. Finally, the Agency's description of its calculation of ED_{01} was not sufficiently detailed to permit the calculations to be repeated. A clear and complete description of the this calculation would significantly improve the transparency and accessibility of the Reassessment.

i) EXPOSURE: The Panel recommends that additional work on the exposure assessment section (as noted in the specific comments) is needed. Specifically, the text and tables describing the source inventory in the Summary are not consistent with the inventory information presented elsewhere in the document, and there needs to be more careful evaluation of the sources of dioxin that make the greatest contribution to dioxin in the food chain.

j) RISKS DUE TO NATURALLY OCCURRING DIOXIN-LIKE CHEMICALS: Because naturally-occurring dioxin-like chemicals can be found in the diet, and presumably in blood and tissue, EPA should explore the magnitude of their biological activity, particularly for questions such as transplacental transport and their ability, *in utero*, to interfere with reproductive development, as has been documented for TCDD itself Most Members were persuaded that some or all constituents of these families of naturally occurring chemicals do not elicit the full spectrum of dioxin-like effects. However, since these chemicals compete for the same Ah receptor as do the 30 listed "dioxin-like chemicals" from industrial and combustion sources (although the binding affinity is much less) and their dose is orders of magnitude greater than that of these 30 agents, the Agency should provide further documentation supporting their position that these chemicals aren't significant. Since the naturally occurring dioxin-like chemicals are in the diet and therefore have a steady-state concentration in blood and tissue, the EPA's belief that the short biologic half-life makes them less biologically active was not found to be convincing and requires additional support.

k) NON-MONOTONIC DOSE RESPONSE FUNCTIONS: There is some evidence that very low doses of dioxin may result in decreases in some adverse responses, including cancer. Although the Panel did not reach any definite conclusions regarding this issue, it does believe that it deserves additional scrutiny. Consequently, the Panel recommends that the totality of evidence concerning this phenomenon, including its potential impact on human health risk, be evaluated more thoroughly by the Agency.

Similarly, any evidence that dioxin can produce adverse effects at extremely low doses, as has been asserted for other substances that affect the endocrine system, should also be carefully evaluated. A recent workshop held by the National Toxicology Program (October 10-12, 2000) to review the low-dose question in the context of endocrine disruptors concluded that such effects are real and no longer controversial (although one Member doubts that this conclusion applies to dioxin).

j) NEED FOR FURTHER INVESTIGATION AND PERIODIC REASSESSMENT: It is important to continue to study and evaluate background levels of this family of chemicals. Even though some Members believe that the current draft assessment may overstate the likely cancer hazard, most believe that non-cancer hazards, such as impaired development, received too little attention in the document. Consistent with basic environmental policy, it is important that EPA continue to try to limit emissions (and human exposure to this class of chemical) in view of the very long biological and environmental persistence of these chemicals.

2 INTRODUCTION

2.1 Background

In April 1991, EPA announced that it would conduct a scientific reassessment of the potential health risks of exposure to dioxin and related compounds. The Agency initiated the reassessment to review emerging scientific knowledge of the biological, human health, and environmental effects of these substances. In particular, EPA evaluated significant advances in the scientific understanding of mechanisms of dioxin toxicity, the carcinogenic and other adverse health effects of dioxin on people, human exposure pathways, and the adverse effects of dioxin on the environment.

The reassessment led to the publication of a multi-volume document titled "Exposure and Human Health Reassessment of 2,3,7,8-Tetrachlorodibenzo-*p*-Dioxin (TCDD) and Related Compounds." The draft of this document was published in 1994. In 1995, this draft was reviewed by EPA's Science Advisory Board (SAB), which issued a 1995 report (EPA-SAB-EC-95-021) with the following four key findings:

a) The review provided substantive comments on two sections in the reassessment documents: the chapter on Dose Response Modeling (Chapter 8) and the Risk Characterization document (identified as Chapter 9 in a previous draft).

b) The review recommended that EPA develop a new chapter on toxicity equivalence factors (TEFs) to consolidate the discussion and scientific information on the use of TEFs for dioxin and related compounds.

c) The review approved the health and exposure sections (Chapters 1–7), stating that there was no need for further SAB review as long as EPA updated these sections with any relevant new information before finalizing them.

d) The review recommended that the revised chapters on Dose Response Modeling and Risk Characterization and the new chapter on TEFs undergo external peer review prior

to the SAB's re-review.

EPA revised the 1994 Reassessment document to address the first three findings listed above and conducted external peer reviews of the revised chapters on Dose Response Modeling (Chapter 8), the updated Integrated Summary and Risk Characterization, and the new chapter on TEFs. After EPA completed further revisions addressing the comments of the several peer review panels, the SAB Dioxin Reassessment Review Subcommittee met on November 1 and 2, 2000 to review those sections of the Reassessment document specified in the 1995 SAB report. Per usual SAB practice, a Charge (see below) for the meeting was developed jointly by EPA staff, SAB staff, and the Chair of the SAB Dioxin Reassessment Review Subcommittee (DRRC). Also, consistent with SAB practice, Members of the DRRC were informed that the Charge was not intended to be exclusive and that additional issues could be introduced by any Member as appropriate.

2.2 Charge

a) **Body Burdens**

(Question 1) Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based on daily dose?

b) **Use of Margin of Exposure Approach**

(Question 2) Has EPA's choice of the MOE approach to risk assessment adequately considered that background levels of the dioxins have dropped dramatically over the past decade, and are continuing to decline? How might the rationale be improved for EPA's decision not to calculate an RfD/RfC, and for the recommended MOE approach for conveying risk information? Is an MOE

approach appropriate, as compared to the traditional RfD/RfC? Should the document present an RfD/RfC?"

(Question 3) The SAB commented that previous dose-response modeling was too limited to biochemical endpoints (CYPIA1, IA2, . . .). Are the calculations of a range of ED_{01} body burden for non-cancer effects in rodents responsive and clearly presented?

Please comment on the weight of evidence interpretation of the body burden data associated with a 1% response rate for non-cancer effects that is presented in Chapter 8, Appendix I and Figure 8-1 (where EPA considers that the data best support a range estimate for ED_{01} body burdens between 10 ng/kg to 50 ng/kg).

c) **Mechanisms and Mode of Action**

(Question 4) How might the discussion of mode of action of dioxin and related compounds be improved?

(Question 5) Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?

d) **Toxicity Equivalence Factors**

(Question 6) Is the history, rationale, and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? Did EPA clearly describe its rationale for recommending adoption of the 1998 World Health Organization TEFs?

(Question7) Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?

e) **Non-cancer Effects**

(Question 8) Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the non-cancer endpoints discussed in the reassessment? Has EPA appropriately defined non-cancer adverse effects and the body burdens associated with them? Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for non-cancer risk assessment for human populations?

(Question 9) Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?

f) **Cancer Effects**

(Question 10 Do you agree with the characterization in this document that dioxin and related compounds are carcinogenic hazards for humans? Does the weight-of-the-evidence support EPA's judgement concerning the listing of environmental dioxins as a likely human carcinogen?

(Question 11) Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the LED_{01} as a point of departure), as described in the EPA "Proposed Guidelines for Carcinogenic Risk Assessment" (EPA/600/P-92/003C; April 1996)? Is this approach equally as valid for dioxin-like compounds? Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for cancer risk assessment for human populations?

(Question12) Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient, or should more weight be given to specific data sources?

g) **Background and Population Exposures**

(Question 13) Have the estimates of background exposures been clearly and reasonably characterized?

(Question 14) Has the relationship between estimating exposures from dietary intake and estimating exposure from body burden been clearly explained and adequately supported? Has EPA adequately considered available models for the low-dose exposure-response relationships (linear, threshold, "J" shaped)?

(Question 15) Have important 'special populations' and age-specific exposures been identified and appropriately characterized?

h) **Children's Risk**

(Question 16) Is the characterization of increased or decreased childhood sensitivity to possible cancer and non-cancer outcomes scientifically supported and reasonable? Is the weight of evidence approach appropriate?

i) **Relative Risks of Breast Feeding**

(Question 17) Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?

j) **Risk Characterization Summary Statement**

(Question 18) Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function

seen in humans and laboratory animals, represent effects of unknown clinical significance, but they may be early indicators of toxic response?

(Question 19) Has the short summary statement in the risk and hazard characterization on page 107 adequately captured the important conclusions, and the areas where further evaluation is needed? What additional points should be made in this short statement?

k) **Sources**

(Question 20) Are these sources adequately described and are the relationships to exposure adequately explained?

l) **General Comments**

(Question 21) Please provide any other comments or suggestions relevant to the two

review documents, as interest and time allow.

3 SPECIFIC FINDINGS[6]

The Panel focused its review on the twenty specific questions in the Charge (Section 2.2), and its comments on each follow. However, before getting into these specific comments from the Panel Members, the reader may benefit from a brief review of some of the overall impressions gained from the Members' reading of the Agency document and their participation in the public review session on Nov. 1 and 2, 2000.

First, the peer-reviewed literature related to dioxin, which is enormous and growing rapidly, is informative on many aspects that need to be considered when assessing actual and potential risks to public health and environmental quality. Second, the Agency document contains a quite thorough and generally objective summarization of that literature. Third, and most important, the available literature does not provide some of the key information needed for quantitative risk assessments for the cancer, non-cancer health, or environmental risks for 2,3,7,8-TCDD, especially in terms of the biological mechanisms between binding to the Ah receptor and ultimate adverse effects. Furthermore, the information gaps are larger for most of the dioxin-like compounds, and their possible synergy, additivity, and/or antagonism to the risks posed by 2,3,7,8-TCDD remain somewhat speculative. Thus, the Agency's risk assessment conclusions were based on some of its “standard models and default assumptions,” which are uncertain, and which tend to be conservative.

This Panel, which includes many Members of the SAB Panel that reviewed an earlier Agency draft in May of 1995, does not see evidence that many of the most critical information gaps will be filled in the next few years (At least one Member believes that little progress in addressing these critical areas was made between 1995 and the current reassessment). It also recognizes that the Agency wishes to, and is obligated to, provide the public with its best current judgment and recommendations on the risks posed to the public and the environment by dioxin and related compounds, and on available means to reduce them. It therefore recommends that the Agency should:

a) Use the comments provided below, as well as the other public comments recently received, to revise substantially, then finalize and publish its dioxin reassessment document, including a thorough review of its uncertainties and limitations regarding its

[6]As in the EPA Reassessment document, the Panel uses the word "dioxin" in this report to mean either the 2,3,7,8-TCDD congener or the ensemble of "dioxin-like" substances with TEFs.

estimation of risks. As noted in the 1995 SAB report, risks predicted by the Agency should include, when possible, quantitative expressions of uncertainty.

b) Develop and implement a research strategy that is focused on the most critical information gaps that currently limit the quantitative evaluation of the risks of dioxin and related compounds.

c) Periodically review the progress of ongoing research on the risks of dioxin and related compounds in order to: 1) reallocate research resources to the most critical issues and best opportunities for progress; and 2) inform the public concerning risks and their minimization.

The remainder of Section 3 addresses the 20 specific questions of the Charge. Please note that the Subcommittee decided to address the questions in what it considered the most logical, rather than numeric, order.

3.1 Body Burdens (Question 1) Did EPA adequately justify its use of body burden as a dose metric for inter-species scaling? Should the document present conclusions based on daily dose?

The first of the two questions is a very important one, relating to many key issues in the reassessment document. Because of large differences between species across cancer and non-cancer endpoints, different dose metrics can lead to widely diverse conclusions. Choosing an appropriate dose metric that allows reasonable animal-to-human extrapolation for different endpoints is an essential element of executing a scientific risk assessment of dioxins. In the latest draft reassessment document, EPA relied heavily on body burden as a single dose metric for inter-species scaling and to interpret epidemiologic observations in occupational or accidental cohorts. Body burden was also used to predict risks for exposure scenarios for the general public. While the justification of this choice was not presented in a manner as clear, consistent, and systematic as the Panel would have preferred, there was a consensus among the Membership that body burden or some other measure of accumulated dose is far more informative than daily dose (mg/Kg/day).

As stated in the draft Reassessment, however, it is not scientifically appropriate to use only one dose metric for inter-species scaling for all toxic effects (Chapter 8, section 8.2.1), i.e., *"It is unlikely*

that a single dose metric will be adequate for interspecies and intraspecies extrapolation for all of these endpoints." This section of the document described in detail the variability in exposure patterns for a variety of potentially or actually exposed human populations as they may relate to cancer and non-cancer end-points. However, this discussion did not include a judicious evaluation of the range of biologically relevant exposure metrics – that is, exposure metrics that are relevant to the various classes of health outcomes (e.g., developmental, reproductive, and neurobehavioral effects). Lacking such evaluation, no convincing reasons were provided for either the Agency's choice of one single dose metric for inter-species scaling, or for body burden as being superior to other dose metrics under all (or most) circumstances.

In any case, body burden as a dose metric can take different forms, such as current body burden, lifetime body burden, peak body burden, average lifetime body burden, average body burden of study period, or steady-state body burden, etc. Section 2.1 of the draft Reassessment addresses some of these body burden metric variants, but they are neither clearly defined nor carefully used throughout the document. The reader has to carefully examine the relevant text to find out its specific meanings. For example, the cancer and non-cancer risk associated with a body burden of 10 mg/Kg that persists for ten days is different than the risks associated with a lifetime body burden of 10 mg/Kg. These are sometimes treated equally in the draft document. To improve clarity, all forms of the body burden metric should be clearly defined, preferably mathematically (in cases where such a formulation is possible), and used specifically and consistently thereafter in the text instead of the general term "body burden." In addition, it is worth noting that body burden is not a traditional dose metric used in pharmacokinetics so its use must be carefully defined throughout the EPA document.

Similarly, other dose metrics are presented to the readers without clear definition, including area under the curve (AUC), peak concentration, administered dose, daily intake, tissue concentration, plasma concentration, blood concentration, adipose tissue concentration, concentration of occupied AhR, induced CYP1A2, and reduced EGFR. All these dose metrics and their interrelations should also be defined clearly in an accompanying table.

In its long-term research program, the Agency should take a systematic approach in its evaluation of the dose metrics. First, objective criteria should be developed for the evaluation of the performance of the various dose metrics. Second, in the evaluation process, important factors relating to inter-species scaling should be considered systematically, including (but not limited to): body weight, fat composition, life- expectancy, exposure scenario, half-life of dioxins and pharmacokinetics of dioxins.

The performance of various dose metrics in inter-species scaling should be evaluated for various health endpoints based on the above factors with existing data. The strengths and weaknesses of the five dose metrics presented in the Integrated Summary were not described in a systematic and comparative manner. The choice of body burden as the dose metric for inter-species scaling would be more convincing if the performances of different dose metrics could be compared using similar criteria, and body burden could be shown to be the better performer.

Using steady-state or average body burden as the dose metric, in general, is justifiable for cumulative long-term health effects. For reproductive and developmental endpoints, it is hard to justify that steady-state or average life time body burden is the best choice. Timing and magnitude of exposures prior to and during critical periods, particularly during perinatal development, are essential for reproductive and developmental outcomes. Using steady-state or average life time body burden will dilute the effects if elevated exposures happened to coincide with the perinatal period, when developmental toxicity is of great concern. For instance, because breast-fed infants receive higher levels of TCDD (from maternal milk) than do formula-fed infants, basing estimated maternal contributions on average lifetime body burden may underestimate the actual dose received by the infant.

Presenting conclusions based on daily dose in the Reassessment document has the advantage that risk assessors and the general public can easily estimate the potential risk based on the average daily intake or background level of dioxin. In both the human epidemiological studies and the animal non-cancer experiments, daily doses are calculated by averaging intakes over a lifetime or the study period. However, it should be made clear to readers of the Reassessment document that, among all the various studies used for risk assessment, only in the animal cancer studies were the daily doses relatively constant, although these doses were generally much higher than daily doses in human studies. The public should also be informed that the upper bound risk for cancer, which is related to daily dose, is an estimate of potential risk having large uncertainties

Overall, the document is not transparent about how averaging was accomplished in the analyses of the epidemiological cohorts or about how a risk assessor should compute an appropriate body burden for an at-risk population exposed to varying daily doses of dioxin. Presentation of a cancer slope factor related to daily dose implies that EPA is considering mostly scenarios in which daily dose is essentially constant over a lifetime and body burden would remain at steady state over most of that lifetime (e.g., after age 35, when steady-state is reached). Of the three epidemiological studies, the BASF cohort (Zober *et al., 1990;* Ott and Zober, 1996) was exposed via a short-term accident. The

method of computing the lifetime average dose for this group should be stated more clearly. These cases are not suited for a steady-state model assumption. EPA should provide a concise statement of how body burdens were computed for all of the observational databases used in the risk assessment, what averaging periods were used, and how a risk assessor should compute a body burden or equivalent average daily dose and dosing period for use in the risk assessment.

3.2 Use of Margin of Exposure Approach

3.2.1 (Question 2) Has EPA's choice of the MOE approach to risk assessment adequately considered that background levels of the dioxins have dropped dramatically over the past decade, and are continuing to decline? How might the rationale be improved for EPA's decision not to calculate an RfD/RfC, and for the recommended MOE approach for conveying risk information? Is an MOE approach appropriate, as compared to the traditional RfD/RfC? Should the document present an RfD/RfC?"

Since EPA presented a slope factor for carcinogenesis, the Panel assumed initially that this question applied exclusively to the assessment of non-cancer endpoints. Although the thrust of the first sub-question was not entirely clear, the Panel also assumed that EPA was concerned that its original rationale for abandoning an RfD/RfC approach in favor of an MOE approach may be eroding as the average levels of dioxin in the environment decline. Most Members of the Panel accept the Agency's observation that setting an RfD or RfC substantially below the estimated current exposure levels would be essentially meaningless for risk management. The MOE approach would therefore be preferred by these Members (at least until estimated exposures drop well below the RfD/RfC values that EPA believes are appropriate). However, when one considers the possibility that background levels are not above the anticipated RfD/RfC, the process of identifying and justifying an RfD could become a useful exercise. As an analogy, the Panel notes that we do not have a RfD for lead because we can't find a no-effect blood level. Instead, we substitute a "level of concern," so the same tactic could be applied to dioxin. If a RfD seems necessary to convey a message or to provide context, as for IRIS, perhaps it could be offered somewhat like the values attached to drinking water contaminants, that is, a version of a maximum contaminant level goal (MCLG).

In short, the process of identifying those studies that detect biologically meaningful effects, as well as the associated doses, would be a useful endeavor that the Agency should pursue. This work

would thus serve as the basis for determining whether background doses really are near those which are likely to pose a serious health hazard. If they are not, then an RfD could be established.

More broadly, some Members of the Panel believe that the MOE approach would be preferable regardless of the levels of ambient exposure because it more properly leaves decisions about the acceptability of a margin of exposure in the hands of risk managers instead of incorporating them through uncertainty factors which are inherent in the RfD/RfC process. That conclusion would logically apply also to substances other than dioxin.

Some Members of the Panel are also concerned that EPA's decision not to provide an RfD/RfC may cause risk managers to neglect non-cancer benefits of diminished dioxin exposure, a point also made by the previous review (SAB, 1995). A compilation of RfDs and RfCs, determined separately for responses of differing severity, would aid risk managers in decisions about the acceptability of risk for various endpoints, perhaps as a function of severity. Such a procedure would parallel the traditional methods for assessing cancer risk, without necessarily adopting the linear no-threshold assumption as a default. When MOEs are very small or non-existent (as EPA argues is the case with dioxin), risk managers need to know how the frequency and severity of sensitive endpoints might respond to additional reductions in average body burdens. Such information is particularly critical in situations where measures to further reduce average body burdens are likely to be costly to the Federal Government, states, and the private sector. The MOE information provided in the reassessment will be more useful to risk managers with the RfD/RfC guidance requested above.

Furthermore, Members of the Panel are concerned about the practical consequences of the absence of RfD/RfC information for dioxin in the EPA's Integrated Risk Information System database (IRIS). Users outside EPA are accustomed to relying upon such information for the assessment of activities involving exposure to chemicals and need to respond to concerns about whether extra protection is needed for non-cancer risks even if the cancer risks of dioxin are managed appropriately. IRIS makes exceptions, however. For lead, it describes the situation as follows: "By comparison to most other environmental toxicants, the degree of uncertainty about the health effects of lead is quite low. It appears that some of these effects, particularly changes in the levels of certain blood enzymes and in aspects of children's neurobehavioral development, may occur at blood lead levels so low as to be essentially without a threshold." The Agency's RfD Work Group discussed inorganic lead (and lead compounds) at two meetings (07/08/1985 and 07/22/1985) and considered it inappropriate to develop an RfD for inorganic lead. Nonetheless, EPA needs to provide guidance to such users on how the

Agency expects risk assessments to be conducted for incremental exposures to dioxin. The document's statements about current MOEs relative to general ambient exposures are not particularly useful in this regard. Furthermore, the document is not transparent about which endpoints would be used to calculate MOEs in a particular exposure situation or how a risk manager should decide on their acceptability.

Some Members think that EPA should either calculate and promulgate an RfD or provide more comment on the "minimal risk" levels promulgated by ATSDR and the World Health Organization (WHO). In 1995, the SAB Committee requested a clear comparison to dioxin-related assessments by other agencies. EPA's response to this request (e.g., the terse treatment on p. 110 of Part III, lines 6-12) is not adequate, in the view of these Members. The document does not explain why ATSDR's "minimal risk" criterion would differ from EPA's unstated criterion. In the case of the WHO position, the document offers no explanation as to why EPA's position is different. No new analysis is necessarily required, but EPA does need to offer a clear explanation of why they are differing from the conclusions of other US and international agencies that have taken official positions on TCDD.

3.2.2 (Question 3) The SAB commented that previous dose-response modeling was too limited to biochemical endpoints (CYPIA1, IA2, . . .). Are the calculations of a range of ED_{01} body burden for non-cancer effects in rodents responsive and clearly presented? Please comment on the weight of evidence interpretation of the body burden data associated with a 1% response rate for non-cancer effects that is presented in Chapter 8, Appendix I and Figure 8-1 (where EPA considers that the data best support a range estimate for ED_{01} body burdens between 10 ng/kg to 50 ng/kg).

Chapter 8 offers the Agency's rationale for choosing the ED_{01} as the basis for evaluating endpoints other than cancer. As it notes, one virtue of the ED_{01} (like other Benchmark doses) is that, for the studies selected, it falls within or near the range of exposures experienced by the organisms studied, and does not require extrapolation to doses remote from that range. Another virtue of the ED_{01}, not possessed by RfDs, is its explicit quantification of the specified effect. The chapter clearly presents the case for the ED_{01} selection and the criteria for inclusion of relevant studies. Limiting this exercise to data presented in tabular form was reasonable. Similarly, the reporting limitations of much of the data in the literature were well noted in the document. Hopefully this will encourage better reporting of data in the future. Because of their much more general use, however, ED_{10} values should be presented, in addition to ED_{01}.

Most of the responses in these studies were reported as continuous effects, as opposed to binary (yes/no) data. For continuous outcomes, the ED_{01} was defined as the dose, d, that satisfies the equation,

(1) $$0.01 = [R(d) - R(0)]/[R(\infty) - R(0)]$$

where R(d) is the mean response at dose d, and $R(\infty)$ is the limiting response as d becomes large. I.e., the ED01 is the dose corresponding to a 1% change in the mean response relative to the limiting change in the mean response.

This definition was implemented using the Hill dose response model,

(2) $$R(d) = b + vd^n/(k^n+d^n), \qquad n \geq 1.$$

The Panel believes the Hill model is an appropriate model for data that exhibit strong evidence of plateau limiting response, and that the restriction $n \geq 1$ is appropriate for avoiding biologically implausible dose responses. However, the Hill dose response model has four parameters and consequently may be too flexible for data for which a plateau is not clearly defined. A reasonable rule would be to use the power model (which is a special case of the Hill model) unless the Hill model provides a statistically significantly better fit to the data.

There are some features of the ED_{01} definition (Equation1), as implemented using the Hill model, that need to be carefully considered. First of all, the ED_{01} is defined as the increase in the mean response divided by the limiting increase, and both numerator and denominator are estimated from the data. One consequence of this is that if, for example, Chemical A causes an increase over background response that is 10 times that of Chemical B at the same experimental doses, the ED01 for these two chemicals are exactly the same (The factor of 10 appears in both the numerator and denominator of (1), and therefore cancels out.). However, with other definitions of the ED01 that have been proposed (e.g., the "hybrid" definition, Gaylor and Slikker, 1990; Kodell and West, 1993; Crump, 1995; NAS, 2000; EPA, 2000; Budtz-Jørgensen *et al.*, 2000) the ED for chemical A would be on the order of 10-fold smaller than that of Chemical B. Careful consideration needs to be given to which type of definition is most appropriate for defining a low dose range of concern for dioxin.

Second, the limiting mean response, R(4), is estimated from the data, and although theoretically there should be such a limiting response, there may be little information in the database regarding this limiting value. As a consequence, when the ED_{01} is estimated from data that are linear in dose (e.g., lie on a straight line), the resulting ED_{01} is infinitely large; this is also generally the case with data that are increasing and convex (upward curving) in dose.[7] Thus, this method is not robust. Moreover, even in cases in which a finite ED_{01} is calculated, these considerations suggest the ED_{01} may be strongly dependent upon the estimate of R(ñ), which in turn is expected to be dependent upon the curvature of the dose response curve at high doses.

To illustrate these issues the Panel conducted a very limited analysis of serum data obtained from male rats in the Kociba *et al.* (1976) study. Table 1 (below) compares ED_{01} in Appendix 1

Table 1 Comparison of ED_{01} Calculations (ng/kg/day) for Serum Analyses in Male Rats (Kociba *et al.*, 1976)

Endpoint	Appendix I	Hybrid Method[a]
Alkaline phosphatase	42	0.51
BUN	NC	0.53
Direct bilirubin	NA	0.43
Indirect bilirubin	NA	0.54
Total bilirubin	550	0.43

NC - BMDS (USEPA 1999) does not calculate excess risk for model selected

NA - Models in BMDS not applicable to these data [a] Hybrid method (Crump 1995; USEPA 1999, 2000; NAS 2000) based on power model, $p_0 = 0.05$, homogeneous variance (Similar or smaller ED01 obtained assuming non-homogeneous variance).

[7]With the Hill equation , $R(d) = b + vd^n/(k^n+d^n)$ and $ED01 = k(0.0101)^{1/n}$. The Hill equation can also be written in the equivalent form, $R(d) = b + ad^n/(1+c^nd^n)$, where $c = 1/k$ and $a = v/k^n$. To make this latter equation linear requires setting $n = 1$ and $c = 0$. However, small (zero) c corresponds to large (infinite) k and consequently large (infinite) ED01. The same conclusion holds for convex curve shapes, except in this case n will be greater than 1. With the alternative equation used in the document, $R(d) = b + sd^n$, the ED01 is always infinite. (Note that this equation is a special case of the Hill equation with $c = 0$.) Thus the method will generally produce infinitely large ED whenever the dose response is linear or convex. Infinite estimates of the ED_{01} occur when applying this method to the dioxin non-cancer data.

of the draft dioxin reassessment with ED_{01} obtained using the hybrid approach. Although the NC and NA designations are not clearly described in the report, it appears to the Panel that in each of is the three cases with these designations, the ED_{01} should be infinite, according to the methodology in the dioxin report. Also, infinity appears just as viable an answer (i.e., associated with as large a likelihood) as the values of 42 ng/kg/day (alkaline phosphatase) and 550 ng/kg/day (total bilirubin) reported in Appendix I. As this table shows, the two methods of calculating ED_{01} produce very different results with these particular data sets. It is not clear from this limited analysis how typical these results are of all the data sets analyzed by the Agency. However, this limited analysis does indicate that a different definition of the ED_{01} can produce very different results from those obtained by the Agency in its analysis.

These considerations suggest that the ED_{01} presently in the document may be highly dependent upon the specific ED estimation method selected by the Agency. Consequently, the Panel believes that the Agency should also calculate ED using other methods, in order to evaluate the effect of the ED method upon the range of body burdens (10 ng/kg to 50 ng/kg) derived from this analysis.

The recently published EPA methodology for calculating water quality criteria (EPA, 2000) recommends the hybrid approach (Gaylor and Slikker, 1990; Kodell and West, 1993; Crump, 1995; Budtz-Jørgensen *et al.*, 2001, EPA, 1999) for calculating benchmark doses (BMDs, another name for EDs) from continuous data, and does not mention the method used by the Agency for dioxin. Likewise, the NAS Committee on methyl mercury (NRC, 2000) after reviewing several methods, also selected a version of the hybrid approach for calculating a BMD for methyl mercury. The Panel recommends that the Agency also calculate ED using the hybrid approach, to enable understanding of the effect upon the resulting ED of the specific method selected by the Agency. This approach could be implemented using the power and Hill models presented in the document.

Regardless of the outcome of this analysis and the final range of body burdens selected by the Agency, further attention needs to be given to explaining how the resulting range is selected. Appendix I, which lists the multiple-dose studies, is cited as the source of the present range. Of the 104 endpoints from the studies selected, 49 show an ED_{01} value below 100 ng/kg. Of these, 29 fall between body burdens of 10 and 50 ng/kg.

Some Panel Members felt that, if the ED01 from the multiple-dose studies are taken at face value, 10-50 ng/kg is a reasonable target range. For policy translation, however, it is critical to also consider the developmental data in Appendix III. Although sparse, they tend to confirm the 10-50 ng/kg range, but they also suggest impaired male reproductive function (such as diminished sperm production) at even lower maternal body burdens. In addition, it is puzzling that the document does not give greater prominence to the developmental data; although some of these consist of single-dose experiments, several administered a range of doses and show dose-response relationships (Gray *et al*, 1997).

Other Panel Members thought the range of 10 to 50 ng/kg was not well supported by the analyses in Appendix I. Simply looking at Figure 8.1, a reader could conclude either that some ED_{01} fall well below 10 ng/kg or that most ED_{01} fall above 50 ng/kg. Moreover, only two of the six categories have median ED_{01} values below 50 ng/kg, and one of those is biochemical changes of uncertain clinical significance. Presumably, EPA is attempting to characterize its uncertainty about a value or values for ED_{01} to use in MOE calculations for risk management. If true, that point should be made more explicit. Further explanation of the choice of the range limits could also be valuable. For example, EPA might conclude that reducing the ED_{01} below 10 ng/kg was not likely to provide significant additional health benefits based on available data, while increasing it above 50 ng/kg would likely lead to a significant incidence of adverse health effects. While making this suggestion, the Panel is not endorsing the numeric values because of the uncertainty of the ED_{01} method itself.

The broad categorization of non-cancer effects from biochemical changes to observed toxic outcomes needs further clarification as to what type of effect is (or should be) given greater consideration when developing relevant quantitative estimates for non-cancer dose ranges. This is of particular importance since many of the biochemical changes measured do not necessarily have a demonstrated link to an adverse outcome. Thus, while some of the non-cancer effects clearly fall within or below the 10 to 50 ng/kg range, this varies dramatically when one compares median body burden ED_{01} values for tissue endpoints versus biochemical changes (Figure 8-1b). For example, the median body burden ED_{01} values for biochemical effects is 25 ng/kg, whereas the median body burden ED_{01} values for hepatic effects is 300 ng/kg and for immune effects 250 ng/kg. Developmental effects for dioxin, given its extraordinarily long half-life, need to be carefully considered, however, and may represent a policy-driven decision point until more studies (particularly with multiple doses versus the single dose studies summarized in Figure 8-2b) are completed and published in the peer-reviewed literature.

Certain implications of body burden (BB) as the dose metric warrant expansion (See also the discussion of body burden as a metric in section 3.1). BB estimates are especially crucial for developmental risk assessments. Fetal and infant exposure are directly dependent on maternal body stores ande profound toxic effects of dioxins are seen as a result of developmental exposure. Although recent data indicate that, grossly, TCDD is distributed relatively uniformly in the rat fetus, closer inspection of brain levels in humans may be warranted. At birth, the human brain is 24% of its adult size. Body weight does not reach 50% of its adult value until after 10 years of age, but by about 6 months of age brain weight is half of adult brain weight (NAS, 1993). Brain-body weight relationships are important to consider because of the high lipid content of brain. About 60% of the structural material of the brain is lipid, and TCDD and related compounds are stored in fat. The brain is a lipid bi-layer rich organ that requires arachidonic (AA) and docosahexanoic (DHA) acids for its structure and function. AA and DHA are also required for the endothelial lining of the blood vessels (Crawford, 2000). These fatty acids are highly susceptible to peroxidation, documented as a major effect of TCDD in brain tissue.

Regarding the evaluation of statistical uncertainty, the document generally reports ED_{01} values and lower confidence limits. At certain points the document evaluates the statistical uncertainty by comparing the ED_{01} estimate to the statistical lower bound. However, these confidence limits are not symmetric about the point estimate; in fact, with the method presently used in the document to compute the ED_{01}, the upper limit on the ED_{01} is infinite with many data sets. Comparison of the upper limit to the lower limit would be a much more reliable measure of the uncertainty in the $ED_{01.}$ The SAB Committee that reviewed the cancer guidelines recommended presenting point estimates and both upper and lower bounds (SAB, 1999). This Panel concurs with that recommendation.

Regarding whether a 1% risk is appropriate for defining the ED, it should be acknowledged that this is mainly a policy decision. This is important with regard to how the resulting ED will be interpreted. Although EPA has generally used 10% in the past, it usually went on to calculate an RfD by application of safety factors. This situation is somewhat different in the present case in that an RfD was not calculated. One practical consideration is that when the ED is used as a risk level the resulting ED should not have an extremely large statistical variation, and should not be extremely model dependent. However, as noted above, the document did not provide statistical confidence intervals for the ED. The document repeatedly notes whether its ED_{01} lies within the experimental doses, apparently using this as a measure of the confidence that can be placed in an estimate. This is not a reliable approach. For example, adding an experimental group at an extremely low dose would be essentially equivalent to increasing the size of the control group. The Panel recommends that statistical confidence limits be calculated and used as an aid in

gauging the uncertainty in the ED. As noted earlier, the Panel recommends that an ED_{10} also be presented because of its common usage.

It is somewhat confusing in Appendix I to see ED_{01} referring to both daily dose and body burden estimates, reported in different units. In Figure 8.1, BB_{01} is used for the latter, which is probably clearer.

3.3 Mechanisms and Mode of Action (Question 4) How might the discussion of mode of action of dioxin and related compounds be improved?

The Panel concluded that the EPA's background chapter on mechanism of action was excellent. Most of the comments were directed to the section under review, the mechanism chapter in the Integrated summary. It was generally felt that this particular chapter was brief for such an important topic, and might not present a full enough picture of the major actions and complexities involved.

There is little discussion of Ah receptor binding in other species that might aid in interpreting the human data. Some detail on the extrapolation from rodent data to human effects involving the Ah receptor in the Reassessment document would be helpful. The discussion below details the molecular differences between the structures of the human and rodent Ah receptor. These differences may significantly alter the activity of the Ah receptor in each species, and, thus, affect our level of confidence in predicting the human response from animal data.

Examination of the amino acid sequence of the murine and human Ah receptors (mAhR/hAhR) reveals a significant level of sequence degeneracy in the carboxyl terminal half. In addition, the hAhR gene is ~42 amino acids longer than the murine AhR. The transactivation domain of the AhR appears to be complex and is composed of an acidic, Q-rich, and P/S/T subdomains. In the extrapolation of ligand binding data from rodents to humans the assumption is made that if ligand binding affinity is similar then the ability of the AhR to activate genes should be similar. Taking into account the high level of sequence degeneracy it is quite possible that the ability of the hAhR to recruit coactivator complexes and thus transactivate genes could be quite different compared with the mAhR both in a quantitative and qualitative sense. Interesting recent reports examining the amino acid sequence of the AhR in the H/W rat and in hamster, which are resistant to TCDD, reveals a high level of degeneracy and restructuring in the transactivation domain (Korkalainen *et al*. (2000). However, the apparent resistance of the hamster and Han/Wistar rat to TCDD is manifested only in adults. In hamsters, it disappears with developmental exposure. In utero administration of TCDD adversely affects growth, reproductive function, and anatomy

in female hamster offspring whose mothers were given a dosage level nearly four orders of magnitude below the dosage level toxic to the adult animal (Wolf *et al.*, 1999). Thus, whether the hAhR is functionally similar to the mAhR requires additional studies, including observations on developmental effects, before a direct extrapolation can be accurately made across species.

The current state of our knowledge of the mechanism of action imposes certain constraints on risk assessment and on models. This fact is mentioned, but reference to specific constraints in the risk assessment modeling and characterization chapters might allow the reader to appreciate the actual impact. These constraints and appropriate references to those chapters should be briefly noted. A figure that illustrates the series of scientific assumptions one needs to make from receptor binding to clear adverse effects is provided in the update document, and should be referenced, as it would be useful in making transparent what is known (and what is unknown) about the mechanism of action.

3.4 Toxicity Equivalence Factors and Toxicity Equivalence Quotients

3.4.1 (Question 6) (a) Is the history, rationale, and support for the TEQ concept, including its limitations and caveats, laid out by EPA in a clear and balanced way in Chapter 9? (b) Did EPA clearly describe its rationale for recommending adoption of the 1998 WHO TEFs?

The first element of this question addresses EPA's presentation of the TEQ concept *per se*.

TEQs provide a basis for calculating the joint biological effects of dioxin-like (AhR binding) chemicals in the environment. A TEQ for a complex mixture is the sum of the concentrations of dioxin-like compounds in the mixture multiplied by their corresponding TEFs, or toxic equivalency factors. That is, the toxic equivalent (TEQ) of a specified mixture equals the sum of the concentrations of the individual congeners multiplied by their potencies relative to 2,3,7,8-TCDD (TEF = 1.0).

Chapter 9 offers a detailed and useful history of the TEF/TEQ concept and its evolution and notes the inevitable uncertainties, which have been widely discussed (e.g., van den Berg *et al*, 2000). In general, the Panel believes that the discussion is clear and balanced, although some Members believe that some important limitations and caveats have not been given sufficient weight. Among these are:

a) In order to obtain TEQ values, a number of assumptions need to be accepted about the TEF approach. Not all of the assumptions are obvious to the reader. Because of the

relatively high magnitude of plausible health risks to the public from dioxin-like chemicals that are described in this report, it is important to convey the assumptions that lead to these numbers.

b) Although the report acknowledges the potential additivity of other chemicals that do not act through the AhR with the PCDD/PCDFs, future revisions of this chapter should do so in more detail by taking account of common endpoints. For example, TCDD and its congeners may affect reproductive fitness through an endocrine mechanism shared with other environmental chemicals such as organochlorine insecticides, phthalates, bisphenol A, and vinclozolin. If male reproductive health, for example, were used as a common endpoint, TEFs with respect to TCDD might be different and more chemicals might need to be included. Conversely, it is acknowledged that at extremely low concentrations, additivity may be of no practical significance. At higher doses, because the shape of the dose-response function may not be monotonic, simple additivity would probably not describe these joint effects accurately.

c) The Panel was divided about the relevance to the TEF/TEQ concept of those naturally occurring chemicals that appear to act through the Ah receptor. The document states that exclusion of endogenous ligands such as those occurring in plants is based on pharmacokinetic principles (e.g., a short biological half-life and consequent lack of bioaccumulation) and the inability of these chemicals to produce a full spectrum of dioxin toxicity.

Some Members argue that the pharmacokinetic argument was not convincing because exposure to these chemicals is on-going and by the time they are eliminated a new dose is received in the next meal (Finley *et al*., 2000). Those Members also noted that, although the binding affinity for the naturally-occurring dioxins is much less than for the 30 chemicals EPA has called dioxin-like **(Will provide reference)**, the overwhelmingly greater concentration of these chemicals in the diet needs to be considered due to their possible role as antagonists. They also note that, given the range of doses in the human diet, perhaps humans have developed adaptive responses to the chemicals which bind to the Ah receptor, thus explaining some of the differences across species. These Members were more persuaded by the claim that some or all constituents of these families of naturally occurring chemicals do not elicit the full spectrum of dioxin-like effects, such as marked adverse effects on postnatal development. Moreover, they argue that the evidence for antagonism comes largely from in vitro experiments; a significant role for

such alleged antagonists has to be established by in vivo studies, especially for sensitive endpoints such as development. Also, their binding affinities for the Ah receptor are relatively low. Finally, some other Members note that the consumption of plant foods is highly variable and episodic within the U.S., so that the continuous renewal argument might not hold Chapter 9 should significantly expand the discussion of naturally occurring AhR ligands.

The second element of question 6 addresses EPA's rationale for recommending adoption of the 1998 WHO TEFs.

Although the Panel does not unanimously accept EPA's rationale (see response to Question 5), all Members agree that it was clearly described.

3.4.2 (Question 7) Does EPA establish clear procedures for using, calculating, and interpreting toxicity equivalence factors?

The Panel reached uniform agreement that the EPA had done an excellent job of summarizing the published work in this area. Based on the quality and number of previous scientific bodies that have evaluated this approach over the years, the Panel agreed that the Agency had made great effort (and achieved considerable success) in addressing the concerns about the development and application of the TEF/TEQ procedure described in the previous SAB report (SAB, 1995). However, there are a number of issues regarding the specifics of the calculations that the Panel believes need amplification.

The Panel also agreed that Chapter 9 does a good job of describing the general framework for calculating TEFs and applying them to obtain a TEQ. However, some important aspects should be described in greater detail. It would be useful to understand better the types of scientific judgments necessary in the implementation of this framework and how such judgments affect the TEF. As suggested by previous reviewers, the Panel agreed that the addition of two examples would be helpful. One set of calculations might illustrate how a set of biological data has been used to calculate a particular TEF. A second set could illustrate how to calculate the TEQ for an environmental sample of a complex mixture (e.g., fly ash). Although such data are sparse, examples of relative potency values (REPs) categorized by response, type of data, and congener, if available, could be included. Such examples would also make the reader aware that a specific compound could have different TEFs for different effects. For example, a compound might have the same maximal enzyme induction level as TCDD (which would suggest a TEF

= 1) but still require a much higher concentration than TCDD to elicit the same enzyme induction level at low doses.

In several places the closeness of the TEF to the (arithmetic) mean of the individual REP values is used to bolster confidence in the TEF. However, it is not clear that the arithmetic mean is a good summary of individual ratios (REPs), which may differ by several orders of magnitude. In many instances the standard deviation of the REP exceeds the mean. The geometric mean may be a better central measure in this situation. For example, the arithmetic mean of 1 and 0.01 is 0.5, whereas the geometric mean of these two REPs is 0.1, which seems like a more reasonable summary value for these ratios. The Panel suggests that the document select a small number of TEFs for comparison to the geometric average of the individual REP as well as the arithmetic average generally used in these calculations.

Another point that deserves mention is the implied assumption that the individual TEFs incorporated into a TEQ have a similar slope in both the observed and unobservable regions of the dose response curve. Although, due to lack of data, this shortcoming cannot be corrected at this time, it introduces a significant simplifying assumption in the approach, which should be acknowledged.

Based on the PCB-related data presented at the public meeting (later determined to be based on the work of Mayes *et al*., 1998). questions were raised about whether the recommended TEF values for selected PCBs are consistent with the experimental carcinogenicity data that are now available on these specific chemicals. Since one of the important foundations for the EPA position that background uptake in the diet poses a significant cancer hazard is based on the TEFs presented in the document, EPA should review these data and make a determination whether a revision of the TEF values for the PCBs is appropriate. This is especially important since PCBs are, in many situations, the predominant source of human exposures.

The Panel also questioned whether the uncertainty in the TEFs and the application of this approach to predicting risks due to current levels of exposure was adequately presented. The Panel recognized that EPA had applied the TEF scheme to 17 PCDDs/PCDFs and 13 PCBs. EPA noted that only five chemicals account for over 70% of the TEQ in the diet (and human blood). Because expert judgment needs to be applied to the data upon which the TEFs were built (due to varying levels of quality in the laboratory analyses), the Panel understands that it is likely that a simple application of probabilistic uncertainty techniques (e.g., Monte Carlo analysis) would not be adequate. As the Agency noted, however, "..the variability of the Relative Potency values found in the literature for these congeners is

much lower than for congeners that are minor contributors to background TEQ. Furthermore, the assigned TEF values for the chemicals contributing 80% to the TEQ intake are similar to the mean of their in vivo REP values." The document could acknowledge the need for better uncertainty analysis in a section devoted to research needs.

Although EPA states that no "proposed method for incorporating quantitative uncertainty descriptors into TEFs received general support or endorsement from the scientific community," recent and forthcoming publications may offer such methods for future updates (e.g., Finley *et al*, 1999). Some Members suggested that, as a follow-up to the Reassessment, the EPA should establish a task force to build "consensus probability density functions" for the thirty chemicals for which TEFs have been established, or to examine related approaches such as those based on fuzzy logic. The recommendations of this task force could then be published in the peer-reviewed literature and, if appropriate, added to the next edition of the EPA Exposure Factors handbook. Incorporating a Monte Carlo analysis to the TEQ calculations could have significant practical importance for sites containing complex mixtures (such as contaminated sediments). See the Appendix, item 1, for further comments on uncertainty analysis for TEFs.

3.4.3 Question 5) Despite the lack of congener-specific data, does the discussion in the Integrated Summary and Risk Characterization support EPA's inference that these effects may occur for all dioxin-like compounds, based on the concept of toxicity equivalence?

Most Members of the Panel believe that the TEF methodology, given the inherent uncertainties stemming from the lack of data, is a reasonable and widely accepted way of dealing with the joint effects of dioxin-like compounds on human health. In support of this view, these Members offer the following observations:

a) Drawing conclusions about environmental health risks solely on the basis of the TCDD component of a mixture would be highly speculative and an inaccurate depiction of the actual risk magnitudes (van den Berg *et al.*, 2000).

b) Contamination by the classes of halogenated aromatic hydrocarbons that include polychlorinated biphenyls (PCBs), dibenzo-p-dioxins (PCDDs), and dibenzofurans (PCDFs) is so ubiquitous that the TEQ strategy has been adopted internationally. Several European countries and Japan now rely on it for risk assessment and risk

management. It enjoys even wider adoption because it is supported and recommended by WHO (van den Berg *et al.*, 1998). Because harmonization of standards with the international community is pursued by U.S. agencies in general, adoption of the WHO TEFs is consistent with those aims.

c) Current TEF values are derived from an extensive literature and have been reviewed by a number of expert panels. The assumption of additivity is also supported by substantial scientific data (e.g., Viluksela *et al.*, 1998).

d) Although the implications of using this approach may, in some circumstances, have a significant impact on the manner in which the regulated community deals with risk assessment and risk management, there are no extant alternative methods that appear to be more appropriate than TEQs for assessing the possible health hazards posed by this family of chemicals as they occur in environmental mixtures.

Other Panel Members remain concerned about various aspects of the TEF methodology as implemented by EPA and are much less convinced that it adequately portrays the toxicity of joint exposures that are not dominated by 2,3,7,8-TCDD. In support of caution with respect to use of the TEF methodology, these Members offer the following arguments:

a) Although it is widely accepted that the binding of TCCD and dioxin- like chemicals to the Ah receptor is a necessary first step in the induction of toxicity, it has been shown by Puga and associates (Puga *et al.*, 2000) that the interaction of TCDD with the Ah receptor alters the expression of over three hundred genes, some increased and some decreased, leading these investigators to conclude that, "Arriving at a sound understanding of the molecular mechanism governing the biological outcome of TCDD exposure promises to be orders of magnitude more complicated than might have been previously imagined." It appears that our understanding of the mechanisms of the diverse forms of TCDD toxicity is very limited. Hence, the judgment as to whether all the TCDD effects may occur with all dioxin-like compounds, as assumed by EPA, cannot be made on theoretical grounds. Although support for such an assumption should come from actual test results, such data are sparse. The document should point to whatever relevant data are available, and the degree to which they are supportive (e.g., Hornung *et al.*, 1996). The issue is closely tied in with the use of the TEQ scheme for evaluation of the

aggregate toxicity of complex mixtures of TCDD and its congeners. The essence of the TEQ approach is that the relative potency for a given congener with respect to TCDD is the same for all the forms of toxicity. Although both the EPA and the Panel recognize that the current basis for this approach is a pragmatic one, and a function of incomplete knowledge, readers of the document may need to be reminded.

b) The vexing problem of different TEFs for different toxic endpoints is illustrated in Table 5-4 in Chapter 5 and Table 2-4 in the Integrated Summary. One chemical, 1,2,3,7,8 - PeCDF, has the same tumorigenic potency as TCDD but is 38 times weaker for teratogenicity; the other congener, 2,3,4,7,8-PeCDF, has half the tumorigenic potency as TCDD, but is 8 times less potent for teratogenicity. These are the only comparisons that can be made from data presented in the assessment document. This hardly provides reassurance that all the forms of toxicity can be lumped into a single Toxicity Equivalent Factor. The co-planar PCBs, in particular, might be different from the PCDDs and PCDFs in this regard. Because TEFs vary among different endpoints as well as congeners, it would also be helpful for the document to note that, as data become available, it may be possible to derive TEQs for different endpoints.

c) As noted in the response to Question 6, the TEQ concept might imply that naturally occurring AhR ligands would elicit toxic responses similar to those found for the dioxin-like compounds of concern to EPA, and because of greater exposure, be more toxicologically important than current levels of the dioxin-like compounds. The lack of evidence for such toxicity casts doubt on the application of the TEQ concept across all 30 dioxin-like chemicals, especially in the presence of so many substances in the diet which bind to the Ah receptor.

d) Another Member noted that the data on many dioxin-like compounds are sparse and often from studies not designed to answer regulatory questions, but that available data suggest (especially for the five compounds most commonly found in humans) that in general, the dioxin-like compounds act in ways very similar to TCDD (at least in that they bind to the Ah receptor, and produce much the same effects, although less effectively). This contention is the basis for the TEQ concept; if it doesn't hold for other compounds, then there is no justification for using TEQs for the whole suite of other compounds. EPA provides good discussion and defense of the use of TEFs. TEFs do, however, need to

be applied with caution, as they are not a biological law, but only an approximation for convenience in handling complex mixtures. As such, their application is perhaps best in site-specific contexts, such as waste cleanup scenarios. While their use in evaluating exposure levels in epidemiology is a convenience, it may lead to error when applied across multiple endpoints. EPA is, however, within bounds of current science to use a judicious TEF approach until such time as a better approach may be developed.

Given the diversity of opinion on the degree to which the TEQ concept can be generalized, some Members of the Panel recommend that EPA explore the feasibility, usefulness and scientific benefits of developing TEFs that differ depending on the health endpoint under consideration. The Panel is aware that such a recommendation implies a research project of significant magnitude, but believes that it also provides a useful model for nearly every situation in which multiple risk factors have to be taken into account. Furthermore, the Panel recommends that EPA continue to examine evidence that could support or contradict the TEF methodology and make adjustments as needed or, if justified, replace the methodology.

3.5 Non-cancer Effects

3.5.1 (Question 8) Have the available human data been adequately integrated with animal information in evaluating likely effect levels for the non-cancer endpoints discussed in the reassessment? Has EPA appropriately defined non-cancer adverse effects and the body burdens associated with them? Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for non-cancer risk assessment for human populations?

EPA is generally confronted with the problem of species extrapolation in situations in which the animal data also must be subjected to dose extrapolation; that is, extrapolation from high experimental exposures to low environmental exposures. For dioxin, the exposure gap is much narrower than usual. However, there are other difficulties that hamper the integration of human and animal data. From the standpoint of sensitivity, the most compatible data sets would be those that embody early developmental, particularly gestational, exposure. In animal studies, TCDD administered during this period induces adverse effects on the nervous, immune, and reproductive systems at dose levels close to the range of human body burdens (Birnbaum *et al.*, 2000; Gray *et al.*, 1997; Mably *et al.*, 1992).

The human information comes from exposures to complex environmental mixtures from which, as the document's summary observes, the contributions of individual chemicals, including TCDD, cannot readily be distinguished (2.2.2.1). In total, however, the human data, as properly noted in the integrated summary, suggests that fetal exposure generally incurs substantially greater health risks than adult exposure. These range from neurodevelopmental deficits to overt structural anomalies, but those occurring at the lowest exposure levels are typically expressed as diminished neurobehavioral test scores. A few Members note, however, that these "neurodevelopmental deficits" may be relevant only to certain PCBs since they have not been shown for all dioxin-like compounds and it is not known what biological mechanism produces these adverse effects. These Members also note that the effects have only been seen consistently at doses well in excess of background levels. Of course, at this point, it is neither possible to state which specific PCB/PCDD/PDCF congeners may be responsible for such effects, nor to describe the underlying mechanisms, but the data are consistent, come from different investigations in different countries, and suggest that this class of chemicals interferes with early brain development. The present Reassessment document correctly describes the current information bearing on this question and draws consistent conclusions.

Animal studies of gestational TCDD exposure have emphasized abnormalities of reproductive function and of the reproductive organs. These consequences are clearly noted in the summary, which points out that the developing male rat seems extremely sensitive to TCDD. It notes that maternal body burdens as low as 50 and 64 ng/kg induce adverse effects, which can be summarized as demasculinization and which include feminization of copulatory behavior. The summary should point out that such effects, indicative of anti-androgenic activity, suggest corresponding effects on brain development, a process extremely sensitive to the actions of gonadal hormones. It is noted, however, that the effects observed in animals may not be appropriate to extend to humans on a quantitative basis since there is virtually no data showing these effects in the many human populations which have been exposed to high doses of these chemicals.

In two arenas, neurotoxicity and reproductive toxicity, compatible human and animal data are sparse. There is limited suggestive evidence that developmental neurotoxicity in humans could occur at background levels of organochlorine mixtures, but even studies focused on PCBs (e.g., Patandin *et al*, 1999) have noted that animal experiments are needed to clarify the individual contributions of PCBs, PCDDs, and PCDFs, and, especially, their interactions. Only a handful of studies have undertaken to examine neurobehavioral endpoints in animals. In both monkeys and rats, the studies show

corresponding patterns of effects, but the doses required to elicit a given effect were considerably lower in the monkey, suggesting they have higher sensitivity (Schantz *et al*., 1989). These data are not cited directly in the integrated summary although it does note that experimental findings point to cognitive effects in animals. A more explicit acknowledgment of the many assumptions inherent in the animal-to-human extrapolation is needed. Currently, the document's text is not adequate to support the document's conclusions that neuro-developmental effects in animals can occur at body burdens in the human exposure range.

The reproductive system anomalies seen in mature animals as the result of developmental exposure have not been investigated in humans, and to do so poses a considerable number of logistical and ethical problems. The integrated summary could, however, more openly point out that some questions about human reproductive effects emerging from the animal experiments will be difficult to answer and that the animal data provide the primary basis for health risk assessment.

The integrated summary presents a set of conclusions drawn from the human and experimental literature. Basically, EPA has used the human data as qualitative support for the observations of non-cancer endpoints in laboratory animals and has not used them to calculate MOEs or any other quantitative measure of toxicity for dioxin. Given the uneven quality of the available human data and some seemingly conflicting findings, most Members of the Panel believe that this level of integration is, at present, appropriate. EPA's conclusions describe the presence of adverse effects as being within or close to the range of current human body burdens. Most Members agree that the authors deserve credit for assembling a sprawling and diversified literature into a coherent document. When revisiting the document, published reports on quantitative relationships between TCDD serum lipid levels and numerous endpoints that include serum hormone and lipid levels should be incorporated into the overall modeling effort or, at the very least, a clear rationale given for their exclusion.

There is also an opportunity using data from the NIOSH cohort to make a direct comparison between rodents and humans. An example that was discussed at the SAB public meeting was the Halperin *et al* (1995) study of the NIOSH cohort measuring caffeine metabolite ratios as a marker for CYP1A2 induction. These investigators found no relationship in this marker in the TCDD-exposed groups. In contrast, the derived ED_{01} body burden for CYP1A2 induction from a study by Tritscher *et al* (1992) was calculated to range from 13 to 19 ng/kg. It should be noted, however, that this

comparison focuses on a biochemical effect that, based on the current data, does not have a demonstrated link to a toxic outcome in either species.

3.5.2 (Question 9) Do reviewers agree with the characterization of human developmental, reproductive, immunological, and endocrinological hazard? What, if any, additional assumptions and uncertainties should EPA embody in these characterizations to make them more explicit?

The document, as written, is a logical presentation of the data on potential developmental, reproductive, immunological, and endocrinological hazards, as derived from experimental data. However, the question is broader than this in that it poses the question as to whether there is a human hazard for any of these endpoints. The summary statement in Section 6 of Part III regarding the human developmental, reproductive, immunological, and endocrinological hazards of dioxin appears to conclude that, although such hazards have not been conclusively demonstrated in humans, EPA presumes they can occur in humans because of their reported occurrence in laboratory animals and the presumed similarities in mechanisms between humans and laboratory animals.

Although some Members of the Panel believe that at least some of these endpoints have in fact been observed in human populations, other Members believe that negative results in some high-exposure human cohorts is evidence against a human hazard for some endpoints, except for developmental toxicity (since the high-exposure studies generally do not involve children or pregnant women). For example, aside from the well known dermatological effects (chloracne) found after extremely high exposures of TCDD, very little morbidity is found even in highly exposed individuals, e.g., the Seveso and Ranch Hand study data. These studies, however, did not seek advanced measures of neurobehavioral function, and the Seveso population showed a marked fall in the ratio of male to female births, indicating a major effect on reproductive integrity (Mocarelli *et al*., 2000). The document would benefit from more transparency in this regard, i.e., present the uncertainties of the human experience along with the "harder" animal data.

Most Members of the Panel agree with the argument that occurrence in animals plus similarity of mechanism is a good argument for the assumption of hazard in humans. Some participants on the Panel believe that so little is known of the mechanisms of action in either animals or humans, it diminishes confidence in the extrapolation. At the same time, however, the Members recognize that such a situation is common in toxicology and not confined merely to dioxin. Members differ in their confidence that animal experiments establish a hazard for specific endpoints or that the postulated mechanisms for those

endpoints are well enough established to be similar in humans and laboratory animals. Members also differ regarding the likelihood that effects observed at relatively high levels of exposure are also possible at lower levels of exposure. That is, assumptions about the nature of the dose- response relationships for these endpoints differ among Panel Members.

There are clearly difficulties in the animal-to-human extrapolations for non-cancer effects, since the acute toxicity observed in animals is much greater than that in humans. The recent case study **(Will provide reference)** involving the female workers who have blood levels in excess of 150,000 ppt, yet exhibit no adverse effects of any sort (other than chloracne) have been observed, seems to support this notion. While the Agency repeatedly suggests that the differences between animals and humans are not significant (probably less than one order of magnitude), it seems to overlook the many studies that suggest much larger differences.**((Will provide reference)**

The most important EPA conclusion, the one regarding toxicity in humans exposed at near background levels (p. 32, lines 18-25, p. 39, lines 15-17), is based on data from the Dutch cohort of children (Patandin *et al*., 1999), but the important limitations of the Dutch studies, noted in Chapter 7B, are not included in EPA's summary. At the EPA's July 2000 Peer Review workshop, Dr. Dickerson's more measured statement about the Dutch studies is that they "..**suggest** (emphasis added) that PCB and other dioxin-like compounds have the potential to retard growth and certain developmental milestones at levels approaching current background." In support of EPA's position, recently published data from the Dutch investigators indicate a positive correlation between dioxin TEQ and the prevalence of coughing, chest congestion, and phlegm, and suggest that the effects of perinatal background exposure to PCBs and dioxins persist into childhood and incur a greater susceptibility to infectious diseases. (Weisglas-Kuperus *et al*., 2000). More data are needed to better understand the effects on children who are exposed early in life.

Endocrine and reproductive effects in adult human males based on occupational cohort studies are ambiguous, so the information (both non-positive and positive) contained in them needs to be carefully described in the characterization. For example, alleged flaws in the Halperin (1998) study of the NIOSH cohort, which indicated negative non-cancer effects, need to be discussed. The animal data, in contrast, and as noted earlier, clearly indicate pronounced impairment of male reproductive function in offspring exposed to fairly low doses *in utero*. Moreover, the Seveso cohort (Mocarelli *et al*, 2000), as described earlier, provides a clear indication of an abnormal ratio in the number of male to female babies

born to fathers that were exposed to high levels of TCDD during adolescence. (This phenomenon is also discussed in section 3.8 of this report.) On the other hand, there are remarkably few effects in this population which includes children, men, and women.

EPA could greatly improve the risk characterization for these endpoints if it added to Part III Figure 8-1from the earlier section of the Reassessment document and the graphic on **(to be provided)** presented by EPA staff at the Public Meeting. These items provide a valuable perspective on the non-cancer health endpoints and should help risk managers in making decisions. Moreover, displaying the human data and animal data in this same way, but in separate figures, would provide additional valuable insight into the strengths and weaknesses of data. The risk manager would also be assisted by displaying frank toxicity data on one figure and data for other effects on another figure.

3.6 Cancer Effects

3.6.1 (Question 11) Part a) Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the LED_{01} as a point of departure), as described in the EPA "Proposed Guidelines for Carcinogenic Risk Assessment" (EPA/600/P-92/003C; April 1996)? Part b)Is this approach equally as valid for dioxin-like compounds? Part c) Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for cancer risk assessment for human populations?

a) **Does the document clearly present the evolving approaches to estimating cancer risk (e.g., margin of exposure and the LED-01 as a point of departure), as described in the EPA "Proposed Guidelines or Carcinogenic Risk Assessment (April 1996)?**

In general, the Panel is satisfied that the document provides a clear explanation of application of the 1996 cancer risk assessment guidelines. A concern was raised that the April 1996 guidelines are only in draft form, which might cause one to believe that the older, 1986 guidelines are in effect. The 1986 guidelines differ from the draft 1996 guidelines on important matters relevant to dioxin (e.g., in the criteria employed for carcinogen classification and in the analytic procedures used in determining cancer slope factors based on epidemiological and animal data). EPA staff made it clear at the Public Meeting that the Agency is seeking advice from SAB on dioxin under the terms of the draft 1996 guidelines.

Overall, there is no reason to believe that the draft 1996 guidelines would be less suitable to dioxin than to other chemicals that EPA assesses for carcinogenic and non-carcinogenic effects. In applying the guidelines to dioxin, the draft document has pooled data from three epidemiological studies, applied linear modeling to these data, and selected the ED_{01} value as a point of departure for assessment of lower doses.

It is not clear whether selection of ED_{10} or ED_{05} instead of ED_{01} would have made a significant difference in the dose-response analysis of the human data. In previous analyses EPA has tended to favor ED_{10}, but in this case the document relies on a lower bound of the ED_{01}, although the rationale for this choice (Part III, p. 82, lines 15-32) is not entirely clear. In previous cases where EPA has used human data to compute a cancer slope factor, the Agency used best estimates of the slope rather than the upper confidence limit. In the case of dioxin, the draft document used the lower confidence limit on ED_{01} as the point of departure for a slope determination based on linear extrapolation to zero dose. The decisions to use ED_{01} instead of ED_{10} and to use the lower confidence limit on the ED_{01} instead of the best estimate of the ED_{01} may have added an additional element of conservatism to the analysis.

A critical issue in applying the guidelines is whether to use the point of departure (in this case the ED_{01}) in a margin-of-exposure (MOE) analysis or as the anchor point for a linear extrapolation to zero dose. The document chose linear extrapolation to zero dose (or at least to doses associated with average background body burdens), a decision that was the subject of considerable discussion at the Public Meeting. The Panel is divided on whether the dose-response analysis of the human data is appropriate given the state of knowledge about dioxin. Some Members are comfortable with the linear extrapolation from the ED_{01}. Some would prefer a nonlinear dose-response model. For example, EPA could consider a model that was both non-linear and included the age-dependent pattern of dosing, without necessarily having a non-zero dose threshold. Non-linearity would also capture the apparent non-linear nature of some of the carcinogenicity data (see Pitot *et al*, 1980) and the widely accepted biological argument that receptor-mediated carcinogens may feature non-linearities or even strict thresholds. And some Members of the Panel would prefer an MOE approach, as was applied to the non-cancer health effects. They see no biological rationale for treating dioxin's cancer effects any differently than the non-cancer effects.

b) **Is this approach equally as valid for dioxin-like compounds?**

The answer to this question hinges on the document's case for the TEF approach, which the Panel addresses in the answers to Questions 6 and 7.

c) **Has EPA appropriately reviewed, characterized, and incorporated the recent epidemiological evidence for cancer risk assessment for human populations?**

This is an important question because (1) EPA has responded to SAB's 1995 recommendation that the agency perform analyses of the recent human data on dioxin; (2) EPA has decided to propose a revised cancer slope factor for dioxin that is based primarily on a new pooled analysis of three occupational cohorts (see Part III, p. 90, lines 8-12); and (3) this is SAB's first opportunity to review EPA's quantitative assessment of the epidemiological data on dioxin.

In general, the Panel was satisfied that the document reviews the relevant epidemiological studies and characterizes their findings appropriately. However, Members of the Panel raised numerous concerns about how the document incorporates the human studies into the quantitative cancer risk assessment. These concerns are not all of equal importance and are not necessarily mutually consistent but their presentation helps explain why the Panel is divided about whether the document has incorporated the epidemiological data into the cancer risk assessment in a scientifically appropriate manner.

First, the occupational studies involving dioxin exposure (as with many human carcinogens) may not be relevant to general population exposures to dioxin and related compounds, as is the case in most epidemiologic studies used for environmental exposures. The Agency needs to discuss in detail how environmental and occupational exposures may differ. The document ultimately applies the revised cancer slope factor derived for dioxin exposures involving inhalation and skin exposures to general population exposures that arise primarily from ingestion of foods containing TCDD and dioxin-like compounds. The workers experiencing these exposures were typically adult males, when first exposed, were exposed for a limited period during their working life, and where usually followed for an average of 10 or 20 years from first exposure . The average body burdens among the highly-exposed workers were estimated to be 10 to 100 times larger than the burdens experienced in the general population. The temporal patterns of exposure were also different, with workers experiencing large peaks and valleys of exposure while the general population exposures are fairly uniform over time. The chemical composition of exposure also differs since the general population is exposed primarily to dioxin-like compounds

(rather than TCDD), while the workers experienced substantial exposures to both TCDD and dioxin-like compounds. The workers experiencing these exposures were typically middle-aged males, yet the general population includes both genders, all ages, and people with varying sensitivities to chemical exposure. It is difficult to be sure of the impact on all segments of a general population and on all cancer outcomes from extrapolating data from workers to all populations.

Second, there are important weaknesses in the NIOSH data, based on the Fingerhut *et al* paper, as demonstrated by Aylward *et al*. (1996).. The data show a very high degree of overlap in estimated internal dose metrics among the 4 NIOSH exposure groups. The values presented in Table 8.2 are body burden estimates, not average lifetime intakes; they are derived from the lifetime average serum lipid concentration estimates reported by the Aylward *et al*. (1996) study. These estimates of internal dose demonstrated, essentially, that "the respiratory tract cancer response in the NIOSH workers is strikingly insensitive to dose." These results, together with the lack of a clear dose response and no consideration of co-exposures to other chemicals, pose considerable caveats in the interpretation of NIOSH cohort study. The only way to resolve these issues would be to attempt a re-analysis of the NIOSH mortality data after reclassification of the exposures for the whole cohort using internal dose estimates as described in Aylward *et al*. Another concern is that Fingerhut *et al*. recognize that there were significant differences in exposure conditions among the 12 plants included in the study, suggesting that the intensity of exposures could have varied significantly, thus weakening the reliability of the "duration of work in a TCDD contamination process" as the metric of exposure. The study did not examine the differential mortality experience across plants as a function of exposure conditions. Since, in this case, the raw data can be obtained, a re-analysis could be conducted.

Third, the pooled analysis that supports the revised cancer slope factor was affected by decisions about which studies to include and exclude. The exclusion of two specific studies (the Ranch Hand cohort and the Seveso population) from the pooled analysis is a source of concern. The document does make a reasonable argument that the non-positive results from the Ranch Hand cohort are statistically compatible with the positive results from the three included cohorts (Part III, pp. 21-22). Yet this argument does not justify exclusion of relevant information from the analysis. Since dose-response modeling takes into account the dose estimates for the exposed populations, the data points for the Ranch Hand and Seveso sub-cohorts would provide information about shape of the dose-response curve, and would also provide more precision in the pooled analysis. It is not clear whether exclusion of these two studies was important since a complete analysis of the five cohorts was not presented in the document. If

data based on accidental exposures to TCDD are to be excluded (e.g., the Seveso population), then data from other exposures dominated by a large accidental release (e.g., the BASF cohort) might also need to be excluded.

Fourth, the document applies linear modeling to data sets that, on visual inspection, do not appear to exhibit linearity of dose response in the observed range (see input data on exposures and SMRs presented in Table 5-2 of the reassessment document). Furthermore, the document did not present the results of goodness-of-fit tests. There is no consistent positive relationship between lifetime average body burden and SMR for all cancer mortality in the data presented in Table 5-2. Since the background rate of all-cancer mortality is large, and the incremental exposures to TCDD are rarely more than a factor of 10 above background, it should be expected that the occupational cohorts will report limited or inconclusive findings, even if TCDD exposure is a potent risk factor for human cancer. One Member takes exception to the above. He believes that all three cohorts do exhibit linearity, in general, when the graphs are based on the original published data. This Member notes that the only really non-linear graph in Table 5-2 is from Aylward, *et al.*, who re-analyzed the NIOSH data using different dose cut-points than the NIOSH investigators. The other graphs of the worker cohorts either appear linear on their face, or in the case of the BASF cohort, have such wide confidence limits around the SMRs that a wide variety of curves could be fit through the data. If anything, the BASF data appear supra-linear at low dose. Consequently, he sees no reason to make the statement above that EPA mis-applies linear modeling to these data.

Fifth, the role of smoking as a possible confounder or synergistic factor is relevant because the primary endpoints evaluated in the document are all cancer mortality and lung cancer mortality. Detailed smoking information is not available for any of the three analyzed cohorts but additional analyses performed in the NIOSH and BASF cohorts suggest that smoking as a confounder is not likely to explain the entire increase in lung cancer. IARC came to a similar conclusion in 1997. The document acknowledges (Part III, p.21, lines 6-7) that "these analyses (of the smoking issue) have not been deemed to be satisfactory by some reviewers of the literature." The revised cancer slope factor for TCDD is biased upward if smoking among workers is at least a partial confounder. Smoking might also operate synergistically with chemical exposure to cause cancer among exposed workers. The document acknowledges this possibility (Part III, p. 21, lines 5-6) and the smoking histories for one of the cohorts presented in chapter 8 (p.8-25) also suggest this possibility. One Member cited a report by Huff *et al*. (1994) on the carcinogenicity of TCDD which asserts that "TCDD is a potent promoter and weak

initiator in multistage models of chemical carcinogenesis." He believes that: a) this is a more accurate statement of the scientific evidence than simply stating that dioxin is a promoter; and b) it also means that speculation about how it might interact with cigarette smoke (which has constituents that are also both initiators and promoters) or its possible synergistic effects are beyond the ability of epidemiologic studies to elucidate. If TCDD and dioxin-like chemicals cause cancer exclusively or primarily among smokers, however, the implications for risk assessment, management, and communication are important.

Sixth, concerns have also been raised about whether other chemical carcinogen exposures in the occupational cohorts could be inducing an inflated cancer slope factor for TCDD. Asbestos and other chemicals are mentioned specifically in the document as possible confounders (Part III, p.21). Perhaps more importantly, the analytic treatment of dioxin-like compounds (non-TCDD TEQ) in the document may have produced an upward bias in the revised cancer slope factor. The BASF and Hamburg cohorts were exposed to substantial amounts of dioxin-like compounds as well as TCDD, yet the dose-response analyses in the document attribute all of the excess cancer mortality to TCDD. In order to be consistent with the TEQ approach advocated in the document, the LED-01 response level attributed to TCDD should have been attributed to TCDD plus the non-TCDD TEQ exposure. It is not clear how much an appropriate adjustment for dioxin-like compounds would reduce the revised cancer slope factor for TCDD.

Seventh, concerns were raised at the July Peer Review Workshop and at the SAB Public meeting that the revised cancer slope factor (cited on p. 90, lines 11-12 in bold) is implausibly large. In order to investigate these concerns, EPA should discuss implied risks among highly exposed workers and community residents that it obtains, using the revised slope factor. These highly exposed populations include various occupational cohorts as well as people experiencing large accidental exposures in Austria, Seveso, Italy and Yusho, Japan. If the implied risks are implausibly large, in light of the actual cancer mortality experience in these populations, EPA should consider revising its slope factor.

An argument advanced in favor of using a low-dose linearity approach is that situations involving incremental doses over background should be modeled with a linear assumption. It is true that a linear approximation would be adequate for small increments to a non-zero dose and non-zero response for a monotonically increasing dose-response function. Yet there is no assurance that the true local dose-response slope near background doses would be the same as the slope calculated from the linear extrapolation down from the lower bound on the ED_{01}. The true slope could be smaller or even larger

than what the draft document estimates. It is also not clear how small the incremental doses would need in order to be able to be to discount the possibility of curvature in the dose-response function near the background dose.

Finally, an alternative approach to analyzing the human data discussed at the Public Meeting would entail a probabilistic analysis of the cancer slope factor using Monte Carlo or other simulation methods. EPA did not perform such an analysis. Their guidelines permit, but do not require, that such an analysis be performed. Although such probabilistic approaches are analytically intensive and are no better than the quality of the inputs used in simulation, they have the advantage of conveying the degree of scientific uncertainty in a slope factor to scientists, risk managers, and the public. They also provide an indication of how much "public health conservatism" is built into any particular slope factor, information about risk that is useful when weighing the benefits and costs of regulatory alternatives and when doing risk communication. A preliminary Monte Carlo analysis of the cancer slope factors was recently presented by Kirman *et al*. (2000).

In summary, the Panel raised significant concerns about whether the document incorporated the epidemiological data into cancer risk assessment in a scientifically appropriate manner. Some of the issues discussed here are also discussed in further detail under Questions 10, 12, and 19.

3.6.2 (Question12) Please comment on the presentation of the range of upper bound risks for the general population based on this reassessment. What alternative approaches should be explored to better characterize quantitative aspects of potential cancer risk? Is the range that is given sufficient, or should more weight be given to specific data sources?

In broad measure, the Panel agrees that the treatment of the range of upper bound risks obtained for the general population in this assessment is consistent with past EPA practice. The available data do not rule out a linear dose response, and a supra-linear response seems implausible. Consequently, the use of a linear response to define the upper bound is not inappropriate and the Panel agrees that the human data are not sufficient to define the dose response shape. The fact that the animal and human data predicted risks in the same range provides some support for the plausibility of the estimates. However, the ranges of results are fairly broad, so it would be surprising if they were not similar.

Nevertheless, the Panel had a number of suggestions regarding the calculation of the range and analyses that could more completely explore the range of upper bound risks. The only dose metric used to calculate ED_{01} from the epidemiology data was average lifetime body burden. It would have been useful to see results using other dose metrics, particularly other metrics based on body burden. To do this would require applying a life table analysis in place of the simple relative risk formula to convert the parameter estimated from the Poisson regression to an estimate of an ED_{01}. Similarly, it would have been helpful to see results of using mechanistic models, such as the two stage model, to extrapolate from the exposure pattern in the epidemiological studies to lifetime exposure. To apply such a model would require EPA to obtain the raw data. Such data are likely available from at least some of these studies (in particular Steenland *et al.*, 1999). Given the importance of these data, it would be appropriate for EPA to acquire this information and conduct a more definitive analysis. Also, reasonable modifications to the analysis should be made to determine their effect upon the range. It appears, for example, from Table 8-2 that a linear model for relative risk was forced through 1 at a dose of zero, which assumes that the comparison population is a valid one. However, based on Table 8-2, this appears questionable, at least for the Hamburg cohort. Although this cohort produced the lowest ED_{01}s, they would have been larger had the background been estimated from the data.

The analysis of the human data in Chapter 8 needs to be explained more fully, and better organized. The calculation of an ED_{01} from each of the three epidemiological studies are described in a single sentence that says only that a linear model was fit using Poisson regression. This is not an adequate description of the fitting process, as numerous types of analyses can fit this description. Additionally, there was no description of how the results of the Poisson regression were converted to ED_{01} estimates. Some of the information in Chapter 10 presumably applies to the analyses in Chapter 8 as well, but this information needs to be incorporated in Chapter 8. Moreover, the description presented in Chapter 10 is also incomplete in some respects and difficult to follow.

Both upper and lower confidence limits on the ED_{01} would help to better characterize the range. Also, some Panel Members thought that calculation of other ED, such as ED_{05}, would be useful. Some Panel Members expressed the view that Monte Carlo analyses would help to understand the range of potential risks. Others thought that, whereas such analyses can be helpful in expressing variability, they have less value in addressing fundamental uncertainty. Recent publications in the peer-reviewed literature have demonstrated the feasibility and utility of applying distributional methods to the assessment of

carcinogenic potency (Evans *et al*, 1994a; Evans *et al*., 1994b). These same kinds of tools are already used to characterize model (mechanistic) uncertainty in other areas of risk assessment (Morgan and Henrion, 1990; Cooke, 1991).

The Panel felt that there needs to be a clearer and more informative statement regarding the appropriate interpretation of the upper bound estimate. In particular, the Panel felt that the statement "This means that there is greater than a 95% chance that cancer risks will be less than the upper bound and could be as low as zero in some individuals." (Chapter 9 page 122, line 11) was inadequate. Such a statement could discuss the linear assumption and provide a brief statement regarding the uncertainty in this assumption.

3.6.3 (Question 10 Do you agree with the characterization in this document that dioxin and related compounds are carcinogenic hazards for humans? Does the weight-of-the-evidence support EPA's judgement concerning the listing of environmental dioxins as a likely human carcinogen?

EPA has adopted criteria for designating a substance as a human cancer hazard in its revised carcinogen risk assessment guidelines (still currently in draft form). In essence, the Agency requires that there be compelling evidence of carcinogenicity in humans or compelling evidence of carcinogenicity in laboratory animals coupled with suggestive evidence of carcinogenicity in humans and similarity of the mode of action in humans and laboratory animals. The criteria for being a likely human carcinogen are somewhat less stringent.

Some of the uncertainty in the Subcommittee on the issue of what constitutes a definite human carcinogen arises from the fact that the Agency has not explained why it shifted from the position in the 1986 Cancer Risk Assessment Guidelines to that in the proposed 1999 Guideline revisions. The 1986 Guidelines requires decisive evidence in humans and animals to categorize an agent as a definite human carcinogen. The proposed Guidelines accept suggestive human evidence, coupled with decisive animal evidence, to assign an agent to the"definite human carcinogen category." It would clarify the issue considerably if the rationale for this change was made clear by the Agency.

The Panel agrees that causal associations have been established between exposure to TCDD and increased cancer incidence for some types of cancers in some species of laboratory animals. The Panel

also agrees that the body of such results is sufficient to satisfy the criterion for compelling evidence of carcinogenicity in laboratory animals for TCDD.

There is a lack of consensus opinion in the Panel with regard to whether TCDD satisfies EPA's 1996 draft cancer Guidelines criteria for a human cancer hazard. There is disagreement about the strength of the epidemiology data as suggestive evidence of carcinogenicity in humans, as well as the scientific data demonstrating similar modes of action in humans and laboratory animals. The diversity of opinion among the Panel Members regarding the strength of the weight of the scientific evidence for the classification of TCDD as a human carcinogen suggests that the available science has significant limitations that the Agency needs to consider in their risk evaluation and to incorporate in their decisions.

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Based on the human epidemiology data, the Members of the Panel cannot dismiss with absolute certainty the assertion that dioxins are not human carcinogens, or accept with complete certainty the position that they are. The Panel Members differ on their confidence that the reported statistically significant associations between exposure and cancer endpoints reported for the occupationally-exposed cohorts can be concluded to be causal. Although all the Panel Members agree that the human epidemiology studies to date have weaknesses (E.g., it would have been helpful if the Agency had discussed the expected differences in epidemiologic results when dealing with genotoxic versus non-genotoxic agents; this would have helped SAB interpret results which may not follow the common patterns of smoking and radiation), those Members who support the classification of TCDD as a human carcinogen consider that the results from studies of TCDD-exposed workers are persuasive and that the variety of studies from researchers in different countries provide limited but convincing evidence of TCDD's carcinogenicity in humans, particularly for lung cancer and even soft tissue sarcomas. Other Panelists consider that the weaknesses and limitations of these studies (e.g., lack of clear dose-response trends, confounding by chemical co-exposures and smoking, lack of a clear mechanism of action for the types of elevated cancers, skepticism regarding the ability of an agent to affect all cancers combined), preclude such classification at this time. One of the epidemiologists on the Panel notes that EPA's discussion in the reassessment document was remiss for not pointing out what findings could be reasonably expected from epidemiologic studies in the case of dioxin. The risks from dioxin might include different cancers in various populations depending on the initiating agents and the timing of exposures. The observed risks would be small because of the interactions of the joint probability distributions. The

only way observed risks would be high is if the group with the initiating exposure is already known, and scrutiny can be directed to the added risk from the promoter. Animal and humans might have different risks because animals have a different set of initiating events. A major problem is that it would be wrong to correct for some of the confounders if indeed the so-called "confounder" can be an initiator of the cancer, as smoking and lung cancer. If true, then correcting for the confounder will interfere with the pathway of cancer. This would prevent the possibility of identifying the risk of the prompter.

With regard to the similarities in mode of action between the human and animal data, some Members of Panel find persuasive EPA's arguments about these similarities, and consider satisfactory the Agency's acknowledgment of the inconsistencies and limitations of the scientific data, and the response to these limitations in support of its position. These Members conclude that TCDD is a multi-species, multi-organ, carcinogen in male and female experimental animals. However, the other Members disagree that key events that precede the cancer response in animals have been observed in humans, and that given the lack of knowledge on the chain of events leading from binding to a receptor to the development of tumors in animals and incongruence in reported responses between the animal laboratory and the human epidemiology studies, it is not possible to conclude that there is similarity of mode of action across species. These Members consider that because of these limitations, TCDD does not deserve to be classified in the same category as cigarette smoke, asbestos, or radon.

As with TCDD, there is lack of consensus on the classification of dioxins and dioxin-like compounds as likely human cancer hazards. In general, the Panel considers that the weight of the evidence in support for such classification of dioxin-like substances is weaker than the data on TCDD. However, some Members of the Panel, agreeing with the classification of TCDD as a human carcinogen, also support classifying dioxins and dioxin-like compounds as likely human carcinogens based on structural similarities and mode of action. Other Panel Members do not support this classification on the basis of the weakness of the supporting data.

As previously stated, the lack of consensus among the Panel Members regarding the strength of weight of the evidence for supporting the classification of TCDD as a human carcinogen, and of dioxins and dioxin-like compounds as likely human carcinogens, is reflective of the limitations of the available scientific data. The Panel recognizes that the Agency has to consider its broader mandate of protecting

the public health when confronted with disagreements in the interpretation of the data and the weight of the evidence on the part of the scientific community. It is important, however, that both the scientific and policy considerations provided in support of such positions be clearly stated.

3.7 Background and Population Exposures

3.7.1 (Question 13) Have the estimates of background exposures been clearly and reasonably characterized?

Overall, the estimates of background exposures, summarized on pp. 70-77 of Part III, have been clearly and reasonably characterized. Moreover, the Reassessment document is thorough and provides an important international resource for assessing exposure to dioxin-like compounds. The data on concentrations in food have been expanded significantly over the 1995 report. Food consumption data have been updated to the most recent CSFII (US Department of Agriculture's Continuing Survey of Food Intake by Individuals) data. This data set is more comprehensive and the EPA made a wise choice to base its analysis of background exposures on these data.

However, there are a few areas in which some revisions should be considered to improve the scientific quality of the document. In particular, the discussion fails to sufficiently describe the continuing controversy about matching observed dioxins concentrations in food to historical and current emissions. There also is a need to specify better the confidence intervals on the value of food-consumption exposures.

Efforts to look not only at food categories but also at diet composition (i.e., a focus on the overall consumption of lipids versus trying to characterize consumption of a specific food type-meat, eggs, milk, etc.) is commendable and should be continued. The science strongly supports the assumption that lipid consumption is the key to understanding intake. In some ways this simplifies the analysis. The variation in fat consumption in human populations is much less than the variation in consumption of any specific food

category. For example, using data from agricultural regions in Germany, WelschPausch and McLachlan (1998) have shown that, when normalized by lipid composition, dioxin compounds had similar lipid-based concentrations in all food media-vegetation, milk, meat, etc. The Panel encourages the EPA to continue to develop data on lipid-based consumption of dioxin-like compounds. Such information, however, is the primary responsibility of other agencies such as the Department of Agriculture and the FDA. The Panel recommends that EPA alert these agencies to the need for such information and that it be shared on a timely basis with the Agency.

The Members of the Panel note that, for dioxin-like compounds, it is appropriate to pool food production among multiple geographical regions. The production and distribution of food within in the US has become, and continues to be, well mixed. It has been shown that TCDD has a long reach. Its characteristic travel distance is on the order of hundreds of km (Bennett *et al*., 1998) this is longer than the mean distance between sources. However, there remains a need to continue to examine seasonal and geographical variation of concentrations of dioxin compounds in local food supplies and how this could impact high-end exposures for some groups-i.e., subsistence fishers and farmers and those who preferentially purchase food from local supplies such as farmers' markets. In addition, the extent and duration of exposures resulting from use of ball clay as a poultry feed additive have not been addressed (although one Member feels that this issue is of minimal nation-wide significance).

When compared to the 1994 Reassessment document, the data on dioxin-like compound concentrations in food provided in the 2000 report are based on much larger data sets and thus are likely to provide a more accurate representation of levels in foods. Nevertheless, these data still lack the geographical and temporal detail to accurately specify the variation of exposures within the US population. The EPA does make clear the limitations of these data, and should work to better characterize these limitations by drawing upon the resources and data of the agencies noted above.

The word "background" (discussed in some detail in a recent paper by Paustenbach (2000)) might be better replaced with "baseline" or "current ambient" to avoid the impression that current exposures are due to natural sources or will continue indefinitely in the future.

3.7.2 (Question 14) Has the relationship between estimating exposures from dietary intake and estimating exposure from body burden been clearly explained and adequately supported? Has EPA adequately considered available models for the low-dose exposure-response relationships (linear, threshold, "J" shaped)?

This question has two components that are for the most part separate issues and are thus dealt with separately in the Panel's response.

a) The first component deals with whether the relationship between estimating exposures from dietary intake and estimating exposure from body burden has been clearly explained and adequately supported.

The relation between tissue levels and dietary intake is described on pp. 70-71 of Part III. A one-compartment steady-state pharmacokinetic model is used, assuming an effective half-life of 7.1 years, that 80% of ingested dioxin is absorbed, and that lipid weight is 25% of the assumed adult body weight of 70 kg. The equation relating tissue levels to dietary intake is

11 pg/g = (65 pg/day x 0.8 absorbed x 7.1 yrs x 365 day/yr) / (0.25 lipid fraction x 70 kg x ln 2) x 1000 g/Kg

This relationship is clearly explained and adequately supported. However, the uncertainty in the parameters and the model inputs should be more clearly emphasized. Due to these uncertainties, the difference between the measured and calculated tissue levels should not be assumed to be significant. The Panel reached general agreement that the Agency has used a reasonable approach to estimate daily uptake of dioxin and dioxin-like compounds. The results that the Agency has obtained are within about a factor of two of that observed in the general population. Thus, it is reasonable that exposure estimates can be based either on assessment of dietary intake or by working backwards from body burdens. These appraisals are certainly reasonable for 2,3,7,8 TCDD, but more data are needed to insure that they are adequate to address all 30 dioxin-like chemicals (due primarily to uncertainty about the biological half-life of these agents).

The predicted and observed lipid burden may be due in part to decreases in dietary levels—that is lipid burdens integrated over long-time periods. But this is not necessarily the only reason for this difference. Other factors should be considered—such as small population size and variability among individuals in diet, fat content, and removal processes. A critical issue for exposure assessment, with respect to risk estimation, is the assumption of simple exponential loss of dioxin from the body following exposure coupled with a 100-fold difference between rodents and humans in biological half-life, the parameter used to characterize such loss. When body burden is used as a metric, a longer half-life translates to a higher body burden and a higher risk for the same daily dose (intake per unit body weight) of dioxin calculated from concentrations in food, water, and air. Conversely, a longer half-life translates to a lower average daily dose when calculated from observed body burdens after exposure in an epidemiology study and a higher risk per unit daily dose. In the case of dioxin, the difference in relative half-lives between humans and animals lead to a substantially higher calculated risk per unit daily dose in humans than predicted with allometric scaling of dose between the species. Some scientists question the values used for the human half-life of dioxin and some cite evidence that half-life may be dose- or body-burden-dependent. Although the document discusses all these issues, the degree of uncertainty in risk that is introduced may not be fully apparent.

Addressing related issues, it appears here that, in the absence of relevant data, a single half-life has been applied to TEQ instead of to the specific congeners. Ideally, the relationship of burden to intake should first be calculated on a congener specific basis then pooled to related TEQ intake to TEQ burden (van der Molen *et al.*, 2000). Unfortunately, this approach is not easily executed because the biologic half-life is know for only a few of the congeners. The Panel recommends using estimates based on the repeated evaluation of blood samples from the Ranch Hand and NIOSH studies, as well as estimates based on first principle (using $K_{o/w}$). This approach, although possessing some uncertainty, is far superior to assuming a half-life for all 30 chemicals that is equal to 2,3,7,8 TCDD simply because that is the only "solid" biologic half-life that is available. During the next five years, however, as an interim process before the next dioxin update in 2005, the Agency could provide periodic updates as the data accumulate.

The Agency for Toxic Substances and Disease Registry chart presented in the Reassessment shows increasing TEQ burden with age. This is explained in the Reassessment by two factors (1)

accumulation with age and (2) changes in exposure with age. A third factor should be considered — changes in removal rates by biochemical processes with age (van der Molen *et al.*, 2000).

Because of the large number of studies that are being conducted of PCDD/PCDFs in the food chain, the Panel expects that it will soon no longer be necessary to rely upon back-calculation from blood levels to estimate daily intake. In light of the many uncertainties associated with back-calculating daily uptake from blood levels, the Panel suggests that the Agency increase the use of complementary field surveys to determine the intake of dioxin-like compounds. Market basket surveys, surveys of home-grown foods, and duplicate diet studies can all be used to estimate the daily uptake of the PCDD/PCDFs. These latter approaches can eliminate the rather large shortcomings of attempting to use body burden to assess daily dose by a back calculation, which is confounded by the long half-life in humans. In particular, actual data on PCDD/PCDF in fatty foods will more readily define whether concentrations in the food chain are dropping or increasing. The Agency, because it is not charged with the responsibility for such analyses, nor is equipped with the necessary resources, should help establish an interagency group, with Agriculture and FDA, to acquire this kind of information

b) The second component of this question deals with low-dose exposure responses.

The actual shape of the low-dose exposure response relation cannot yet be determined from the available data. Some Members believe that there may be evidence for anti-carcinogenicity of TCDD at low doses in the animal studies, and that EPA should have been more forthcoming about that evidence. The 1995 SAB review asked EPA to evaluate evidence related to low dose exposures, and it has done so on pages 29-30 of Part III. In the view of some Panel Members, the discussion there should be more complete and consider what is known about the promoter-like characteristics of 2,3,7,8 TCDD. For example, the Kociba (1978) study actually showed a deficit for all tumors combined in all dose groups in comparison to the controls. That finding is statistically significant for the lowest two dose groups, and deficits in uterine, mammary, and pituitary tumors in female rats and pancreatic and adrenal tumors in male rats are statistically significant in the highest dose group. If the analysis is restricted to all malignant tumors, the data show statistically significant deficits at the lower two doses and a statistically significant increase only at the highest dose (Kociba, 1992). The EPA document discounts most of the deficits as related to significant weight loss, but does not offer an explanation for the mammary tumor deficit. It also

does not discuss the implications of significant weight loss on the evaluation of maximally tolerated dose. Without the highest dose, the Kociba experiment would have been judged negative. Kociba's own conclusion was that the data "indicate that doses of TCDD sufficient to induce severe toxicity increased the incidence of some types of neoplasms in rats, while reducing the incidence of other types." Similarly, in the Pitot *et al*. (1987) study, the investigators examined the numbers and size of altered hepatic foci (AHF) in livers of adult female rats. The authors concluded in the abstract of the paper that "At several sub-threshold doses of PB and TCDD an inhibition of AHF formation and growth . . . was observed." These findings from Kociba *et al* (1978) and Pitot *et al* (1987) suggest to some Members that TCDD might be a net carcinogen at higher exposures but a net anti-carcinogen at lower exposures, raising the possibility that TCDD would be an anti-carcinogen in the human population at current levels of exposure. However, one participant pointed out that it was subsequently revealed that the control animals in the Pitot *et al*. (1987) experiment were not concurrent controls and were older than the treated animals (Portier *et al.*, 1996). This information diminishes the evidence for inhibition found in this particular study. EPA should acknowledge the possibility that reducing current body burdens of TCDD might lead to no change at all in cancer incidence, or even a net increase. Given the uncertainty in the data , the Panel agrees that choice of complex models cannot be justified (at this time.

For this reason some Panel Members believe that it is to apply the MOE approach to both cancer and non-cancer responses.

3.7.3 (Question 15) Have important 'special populations' and age-specific exposures been identified and appropriately characterized?

Populations at increased risk from exposure to dioxin and dioxin-like compounds include those subgroups that may be at the high end of the exposure distributions as well as the biologically more susceptible. EPA has appropriately identified several populations as having the potential to be highly exposed. These populations include nursing infants, individuals with unique diets, occupationally exposed individuals, cigarette smokers, and individuals who may live near significant sources. Some Panel Members believe that biologically susceptible populations could include individuals that are at increased risk because of age or gender, or some other population characteristic-specific effect, as well as those individuals that could be genetically susceptible (e.g., may express the Ah receptor more that others).

The Reassessment Document did a credible job of identifying those at increased risk because of demographic characteristics; there was very limited information available on genetic susceptibility. Some further discussion of genetic predisposition and special dietary preferences or limitations (e.g., subsistence fishing) would be desirable.

The exposure of nursing infants was discussed in detail. Other populations were discussed qualitatively, but not quantitatively, since few data seem to be available for a quantitative assessment. However, EPA should include, if possible, all "special populations" in the Summary Document. It is possible that the Native American population may be be more highly exposed than other populations because of its culture that relies on harvesting fish, game, etc., as an important part of the diet. Thus, they should be mentioned explicitly, and separately, from sport anglers in the Summary. Women of childbearing age, as well as younger females, are a special population of concern because any exposure they receive may be passed to their children through breast milk or transplacentally. In addition, and as recognized in the Reassessment Document, breast milk is an important excretion route for persistent chemicals stored in fat and bone. The fetus may also represent an excretion route, as it apparently is for methyl mercury (Amin-Zaki *et al.*, 1979). Therefore, nulliparous women and women who do not breast feed may be also a population at risk, with body burdens consistent with those of the male population. The estimated life-long risk for multipara and women who breast feed could be significantly lower than for the previous subgroup. Although these issues are mentioned in the document, and in parts of the Summary, they are not translated into a differential risk assessment for the specific male and female population subgroups.

EPA provided information on body burdens of dioxin. However, it should also provide additional information on how body burdens vary with age, on how body burden varies in females depending on the number of offspring, how they may vary for the significant proportion of the population on weight-loss diets, and how therapeutic drugs may effect body burdens. EPA should also identify important data gaps in this area (e.g. body burdens in post-menopausal women) to highlight research opportunities.

Information was provided about the range of exposures (as characterized by ranges in serum blood levels) in the general population. However, EPA did not evaluate if the individuals at the higher end of this range were in the category of "special populations" with higher exposures. For example, the high

range of general population exposures could be representative of individuals such as those with unique diets or those living near unique sources. Without additional analyses EPA's statement that "These kinds of exposures [e.g., highly exposed populations] are addressed within the estimates of variability of background and are not considered to result in highly exposed populations" may not be valid. Three studies examining the effect of fish consumption on PCB blood levels are mentioned, two of them showing elevated levels in those eating large amounts of fish; these studies appear to contradict EPA's assumption. A few other studies that examined the exposure of people eating local or homegrown produce near a dioxin source also showed elevated exposure levels.

The Panel's response to Question 11 also includes information related to this question.

3.8 Children's Risk (Question 16) Is the characterization of increased or decreased childhood sensitivity to possible cancer and non-cancer outcomes scientifically supported and reasonable? Is the weight of evidence approach appropriate?

The draft Reassessment's characterization of increased or decreased childhood sensitivity to possible cancer and non-cancer outcomes should be improved. In regard to cancer endpoints, the Agency accurately portrays the lack of studies that can address this question. However, in the SAB's review of the proposed cancer guidelines for children, the Panel indicated that when a chemical's mechanism of action is proposed and discussed, the Agency should identify all the critical steps in the mechanism and identify what is known about these steps (proteins, receptors) in the developing human (SAB, 2000). For example, if a mechanism of action of TCDD is through the Ah receptor, the Agency should identify what is known about these critical steps in the developing human. This was not done in the draft Reassessment.

With regard to non-cancer endpoints, the best data to show that the developing human may have altered and increased sensitivity to dioxins comes from the Italian (Seveso) studies demonstrating a decrease in the offspring ratio of males to females born to adult males exposed to high levels of TCDD (Mocarelli *et al*., 2000). The same investigators also demonstrated that, if the exposure occurred during adolescence as compared to adulthood, the altered ratio of offspring appears to continue even after the body burden of TCDD decreases – if the human male is exposed during the developmental period. However, if exposure occurred later in life, the gender ratio of the offspring returns to normal after the

body burden decreases. This period of increased sensitivity of the human during development to long term alteration of the gender ratio was recently confirmed in the Austrian cohort of workers exposed to dioxin **(Will provide reference)**. These data are critical in understanding the risks of dioxins to children, infants, and the fetus. One Members asks, however, if dioxin does indeed have the capacity to adversely affect the developing organism, why is that other adverse effects have not be reported for the young children who were exposed at Seveso or Times Beach? He believes therefore, that the Agency should acknowledge that although the Seveso data on the sex ratio change is newsworthy, additional studies are needed to assess whether fetuses or children are genuinely particularly sensitive to the acute or chronic effects of TCDD or related chemicals.

It is very important that, in the draft Reassessment document, the Agency clearly indicates when the subject under discussion is TCDD, dioxins, or dioxin - like substances. Although the document is comprehensible to the careful reader who is familiar with the data, it is not clear to the less informed reader, and this may lead to confusion and the formation of possibly unsupported conclusions.

3.9 Relative Risks of Breast Feeding (Question 17) Has EPA adequately characterized how nursing affects short-term and long-term body burdens of dioxins and related compounds?

EPA summarized the data from studies that compared dioxin levels in infants who have been breast-fed with those who have been formula fed. EPA also calculated dioxin intakes for nursing infants using time dependent values for breast milk concentrations, consumption rates and body weights. It also calculated changes in body burden over time using a one-compartment, first-order pharmacokinetic model. The nursing scenarios included in the modeling were: formula only, 6 weeks nursing, 6 months nursing and one year. It also did a sensitivity analysis to test the assumptions about changes in breast milk concentrations and half-life over time.

It is recommended that the exposure scenarios be extended beyond one year to include the subgroup of committed breast-feeders and other women that extend breast feeding beyond one year (e.g., up to three years) because of cultural reasons. It would also be useful to consider the changes in milk composition during the first month post-partum. The milk supply is not well established until the third week or so following birth. During the first week, milk secretion consist mainly of colostrum which is very

low in fat and, consequently, in fat-soluble compounds. Fat content increases significantly and quickly after the first week, peaking and then decreasing also very quickly during the following few weeks, and more slowly thereafter. There is a two-week or so window, therefore, of high fat excretion in the first month following parturition that may need to be examined in more detail, especially as it may bear on non-cancer, developmental effects. In addition, the summary of the extant data on breast feeding strongly suggests that dioxin and dioxin-like compound intake and contribution to body burden for breast-feeding infants decreases significantly with birth order, so it cannot be assumed that risk is uniform for all children. EPA should consider first born children at higher risk of increased intake than later-borne siblings. The age of the mother at first birth could be an additional risk factor because older women would be more likely to have reached higher steady state body burdens than younger women.

EPA used the studies and modeling results to describe intakes and body burdens of infants over time. It included a graph displaying these data, and this addition is an important contribution to this characterization. EPA should incorporate information about blood levels from the German studies into the first paragraph of this section on page 74 of the Risk Summary. Those data place the modeling results into context.

The characterization of cancer health risks to nursing infants was adequate, with the caveats expressed above regarding birth order. However, some Members of the Panel believe that EPA could have been more direct in noting that a putative human carcinogen or tumor promoter such as dioxin will not result in higher lifetime risks of cancer for exposure in childhood as compared with exposures during adulthood, even after adjusting for the temporarily higher doses received during childhood.

The Panel is perplexed at the minimal characterization of non-cancer health risks for infants and children, especially in contrast to the effort devoted to cancer. This is a very significant and obvious omission, and a concern for the Panel, particularly considering the data available on developmental and reproductive effects. EPA has evaluated non-cancer health risks in detail and should use the knowledge it has gained to complete the risk characterization for this special population. Staff in state and local health departments, physicians, women considering nursing etc., will want information about those risks and may not have the time or expertise to review the necessary data to complete this characterization. EPA is referred to the response to Question 19 of the Charge regarding non-cancer health effects.

3.10 Risk Characterization Summary Statement

3.10.1 (Question 18) Does the summary and analysis support the conclusion that enzyme induction, changes in hormone levels, and indicators of altered cellular function seen in humans and laboratory animals, represent effects of unknown clinical significance, but they may be early indicators of toxic response?

The health significance of small background perturbations of enzyme and hormone level usually gets discussed under the heading of adaptive and compensatory responses. Adaptation is a physiological response to normal forms of stress like muscular hypertrophy with exercise or increased sweating with chronic exposure to heat. Compensatory responses are efforts by the body to cope with a stressful event. Sometimes there are ambiguities in the distinction between adaptation and compensation, since adaptive responses in one circumstance may be a compensatory response in another; for example, hypertrophy of one kidney in response to the loss of the other kidney. The Panel supports the position that non-stochastic processes like those induced by dioxin are graded in character. At higher doses there are strong multiple effects. With diminishing dose levels, the range of effects narrows and their intensity decreases. As noted by some Members, small effects like perturbations in enzyme and hormone levels may be anticipated at low doses, and there may be ambiguity as to whether these effects are adaptive or compensator; in either case they may not necessarily be detrimental. In the absence of information to the contrary, some Members of the Panel thought that they should be regarded as evidence of mild toxicity.

The Members were divided about the health significance of such changes. Several Panel Members were uncomfortable with the statement that effects such as enzyme induction, changes in hormone levels and indicators of altered cellular function may be early indicators of toxic response. By that reasoning, virtually any xenobiotic, and many ordinary human activities, would qualify as potentially toxic, and normal human variability would be seen as potentially pathologic. These Members would be more comfortable if the statement simply ended with the more neutral observation that such changes are of unknown clinical significance. If EPA continues to use the "early indicator" language, it should be balanced in the same paragraph with the possibility that such changes are simply adaptive responses.

At least one Panel Member also supported the position that enzyme induction, changes in hormone levels and indicators of altered cellular function seen in humans and laboratory animals are not necessarily valid as indicators of toxic responses. Based largely on the analysis of TCDD- dependent induction of thymic atrophy and cleft palate in inbred mice (Poland and Glover, 1980) and by numerous dose-response and structure activity relationship studies, it is widely accepted that the Ah receptor is associated with many of the toxic responses (including cancer) elicited by TCDD in animals. Two benchmark studies clearly show, however, that the Ah receptor is obligatory, but not sufficient, for the induction of epidermal hyperkeratinization (Knutson and Poland, 1982) in mice and a putative human carcinogen (Poland *et al*, 1982). These responses were shown to segregate with two genetic loci, Ah and hr. The significance of these studies is that Ah receptor mediated biochemical changes (e.g., induction of CYP1A1) can occur without resulting in local epidermal toxicity unless there is a genetic susceptibility. This offers some evidence in animal models against the continuum of responses hypothesis for at least certain biochemical changes.

The clinical changes observed in human populations have not been definitive to date with regard to their relevance to toxic endpoints of major concern. However, a caveat that needs to be included is the ability to assess the impact of chronic exposure on development. The studies that have been conducted on industrially exposed populations (BASF, NIOSH) and on Viet Nam veterans (Ranch Hand) do not provide information useful in assessing potential adverse developmental outcomes. However, study of the Seveso and Times Beach cohorts may be insightful.

3.10.2 (Question 19) Has the short summary statement in the risk and hazard characterization on page 122 adequately captured the important conclusions, and the areas where further evaluation is needed? What additional points should be made in this short statement?

The Summary Statement is a very important part of the document, since it is the only place that non-technical readers, including risk managers, can get an overview of the assessment and its conclusions. Some Members of the Panel found that the summary statement was too one-sided in failing to adequately present the full range of legitimate opinion about the interpretation of the evidence for dioxin as a human carcinogen. The bottom line of the current risk assessment is a flat-out position that dioxin is a human

carcinogen and that current body burdens are dangerous, particularly for children, genetically sensitive persons, and those whose diet enhances their exposure.

The EPA's dioxin assessment document advocates a linear non-threshold extrapolation model although it takes a strong position that the initial pathway for all forms of toxicity is mediated by the Ah receptor. Some Members believe that receptor mechanisms often entail non-linear phenomena that may cause the dose-response relationship to fall faster than linearly with decreasing dose. Some Panel Members believe that the estimated cancer risks at small doses are bound to be lower with the receptor-mediated process than with the linear model.

The Panel recommends that complete reliance on the upper confidence limit (based on EPA's standard models and defaults) for quantitative risk assessment of cancer risks needs to be tempered. Upper confidence limits deal with the question of "how bad can the risks be." Given the current questions about how much more regulatory action is appropriate for dioxin, there is a legitimate need to also include "best estimates" of the cancer risk, and even a "lower" risk estimate that are not solely reliant on a linear model. The summary might also point out that with a receptor mediated cancer process, the best estimate of risk from the linear non-threshold model is already an "upper limit."

As discussed in Section 3.2.1, the logic in the summary for dismissing RfD/RfC values as "uninformative for safety" is hard to understand. The present concern is how low do body burdens of dioxin need to be for safety. That calls for RfD/RfCs. Why not include them, even if they entail lower body burdens than are current? If, in fact, the RfD is lower than the background dose, itwould provide a target for regulatory action. The practical value of the MOE approach for risk managers, as pointed out by materials submitted by the Japan Environment Institute (2000) as public comment, is unclear. At the same time, these values should be compared with the way IRIS handles lead, which also, by conventional methods, would show a RfD lower than current exposure levels.

No new methodologies are needed to identify an RfD for the 2,3,7,8-TCDD or the other congeners. One useful procedure that would be easy to implement would be to calculate ED_{10}s as well as ED_{01}s. Then, applying the usual uncertainty factors (UFs) used with Benchmark Doses, or BMD_{10} values, provide RfDs for as many of the specific dioxins and PCBs as possible.

As the report acknowledges in many places, its conclusions are based on a number of implicit and explicit assumptions. The Panel recommends that these be assembled in a statement or list that also uses them to indicate significant lacunae in data and those questions for which additional research is most urgently needed.

The document's discussion of the biology of TCDD and dioxin-like compounds does not provide a sound basis for using models of different low-dose shape to characterize cancer and non-cancer endpoints. The Panel consequently recommends that cancer effects be treated in the same way as the non-cancer effects, i.e., by reporting both an ED_{01} and an RfD, and not cancer risk estimates from low exposures.

3.11 Sources (Question 20) Are these sources adequately described and are the relationships to exposure adequately explained?

The Inventory of Dioxin Sources is an outstanding compilation of available information on dioxin sources. The Agency is commended for this effort. The presentation of the inventory results is, however, somewhat confusing, for two reasons: a) the exclusion of the so-called "unquantified" sources from the main description of the sources; and b) the lack of consistency of the Summary Document (Part III) with the Sources Inventory.

Part III presents the emission inventory in 3 tables:

a) the "quantitative" inventory in Table 4-2, p. 135
b) the so-called "un-quantified" sources in Table 4-3 (all of which are in fact quantified in that table)
c) the "unquantifiable" sources in Table 4-4

The 1998 peer review of "The Inventory of Sources of Dioxin in the United States" concluded that this approach of presenting the better quantified sources as the de facto main inventory "presents a potentially misleading picture of the results of the emissions inventory (Executive Summary, p. v)."

Notable in Table 4-3 are landfill fires, with estimated emissions of 1050 g TEQ (p. 137). This is comparable to emissions from municipal waste incineration, listed in Table 4-2 as the largest source of dioxin emissions.

The text and tables describing the source inventory in the Summary are not consistent with the inventory information presented elsewhere in the document. In Table 4-2, Part III, backyard barrel burning does not appear, nor does it appear in Table 4-3 of "un-quantified sources" (where forest and brush fires again appear, the only source to be counted in both the quantified and un-quantified source emission tables). Nor does it appear in Table 4-4 listing "sources that are currently unquantifiable." However, on p. 61 Part III, it is stated that "70% of all "quantifiable" environmental releases in 1995 were contributed by emissions to air from just three source categories: municipal waste incinerators, backyard burning of refuse in barrels, and medical waste." Clearly this text refers to the source inventory given in the Source Inventory Document, not the inventory presented in Part III.

The discussion of the relation of sources to exposure is presented on pages 65 and 66 of Part III, and can be summarized as follows:

a) "It is unlikely that emission rates of CDD/CDFs from known sources correlate proportionally with general population exposures (pp. 65-66).

b) "..at least one third of the overall risk from dioxin-like compounds comes from reservoir sources," that 1/3 of the general population TEQ exposure is due to PCBs, and that human exposure to the dioxin-like PCBs is thought to be derived almost completely from reservoir sources (p. 66).

c) "..much of the agricultural areas that produce dietary animal fats are not located near or directly downwind of the major sources of dioxin and related compounds."(p. 66)

EPA implies that the sources of contributions to the exposure of the general population are not in the same proportion as their contribution to the general environment. Nevertheless, in the absence of explicit analysis indicating how these emission sources contribute to exposure, the overall implication from

the document is that sources should be subject to regulatory action in proportion to their contribution to emissions, even when exposures to the general population may be affected only minimally.

This issue could be resolved through developing a better understanding of the biologic half-life in humans of the 30 dioxin-like chemicals. This can be estimated from the NIOSH or Seveso cohorts, since their blood has been sampled several times. With these data, one can couple the concentration data in foods with the biologic half-life information to predict the steady state blood levels for U.S. residents. This would allow one to understand whether emission rates and sources of the dioxins have been properly characterized.

The primarily negative statements quoted above could be rephrased positively. Specifically, those sources located near or upwind of agricultural areas that produce dietary and animal fats are likely to make the largest contributions to exposure. However, the significance of the un-quantified reservoir contributions raise important questions in terms of future Agency actions that should be addressed clearly in the Summary. First, it would be useful to provide some estimate of the impact on exposure of a reduction in quantifiable source emissions. Second, as the known source emission reductions take place (even when no regulatory action is taken), the relative contribution of the reservoir sources to general population exposure will increase, so that source controls become less and less effective for risk reduction. There has to be, therefore, an effort at understanding the nature of reservoir sources, and their relationship to past, current, and future environmental concentrations.

APPENDIX

Uncertainty/Monte Carlo Analysis re TEF

Some Members of the Panel noted that the conclusions of the Reassessment are based on what is known about the uptake of the 30 dioxin-like chemicals in the diet and their respective TEFs. 2, 3, 7, 8 TCDD is the only chemical for which a great deal is known, yet only 10% of the background dose (TEQ) is due to this congener. Considering the uncertainty in the selection of the TEFs (as discussed in the reassessment and presented in Finley (1999), as well as the distribution of values for these same chemicals in the diet (Finley *et al.*, 2000a,b), some Panel Members believe that the EPA could provide a much more informed conclusion about the public health risk, even if it was a preliminary "default" Monte Carlo approach like the one used by Finley *et al*. (1999) For example, it appears that there is sufficient information to allow the Agency to be able to quantitatively characterize (approximate) the risks for the entire population e.g., the 50th, 95th and 99th percentile. Although uncertain, this characterization would be much more informative than the text in the current draft of the Reassessment.

Given that so much of the total TEQ in the diet is due to the PCBs and due to the variability in the data underpinning the TEFs for the PCBs, one Member predicted that, based on his experience, the results of such an analyses might indicate that the 50th percentile of the population may well be exposed to theoretical cancer risks in the region of 1 in 10,000 to 1 in 50,000 (rather than the 1 in 1,000 value suggested by EPA.

It is feasible to undertake a quantitative uncertainty analysis of the cancer slope factor using methods demonstrated in the peer-reviewed literature (Evans *et al*, 1994a; Evans *et al*., 1994b). One Member expects that, if such an analysis were conducted, his expectation is that the 50th percentile risks could be as low as 1 in 100,000 and might well be less. Again, such a characterization gives a much different impression than the Agency's current risk characterization that "cancer risks in the general population may be as great as 1 in 1,000." It is suggested that EPA at least provide even a limited uncertainty analysis of the uncertainty in their risk estimates of the background risks.

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